



MEETING REPORT

WHO Expert Consultation meeting on Antimicrobial Resistance (AMR) Health Burden Estimation

18-19 January 2018

Geneva, Switzerland, WHO HQ

Executive summary

The WHO Global Burden of Disease (GBD)¹ project provides a framework for integrating, validating, analysing and disseminating information to assess the comparative importance of diseases, injuries and risk factors in causing premature death, loss of health and disability in different populations. The study has introduced a new metric –disability-adjusted life-years (DALY) – as a single measure to quantify the burden of diseases (BOD). Countries can combine this type of evidence, along with information about policies and their costs, to decide how to set their health agenda. However, data on mortality and health are often fragmented and inconsistent. In particular, comprehensive data on the health burden of antimicrobial resistance (AMR) are still extraordinarily difficult to obtain.

The WHO Global Antimicrobial Resistance surveillance System (GLASS) is collecting information of frequency of AMR in selected bacterial pathogens², but in order to assess AMR BOD additional information is needed. In this context, WHO's AMR Surveillance team has prioritized in its current GLASS work plan the study development and capacity-building for improved evaluation of the burden of AMR. What is needed now is a more comprehensive set of epidemiological data to estimate the AMR health impact according to a standardized methodology to collect and analyse these data. Two, first steps were taken by GLASS to start addressing this issue:

- In collaboration with the WHO Collaborating Centre (CC) at the Geneva University Hospitals, the Universities of Tübingen and Verona were commissioned to carry out a literature review on current research designs for and challenges in adequate data collection and assessment of the clinical and health burden of AMR.
- An expert consultation meeting on AMR health burden estimation was organised to discuss the focused literature review and how the WHO can and should initiate more comprehensive data collection in order to develop robust BOD estimates for AMR.

¹ http://www.who.int/healthinfo/global_burden_disease/about/en/

² <http://www.who.int/glass/resources/publications/early-implementation-report/en/>

Accurate data on the economic and health burden of AMR is needed by governments to effectively prioritise their public health spending. Furthermore, robust data are valuable for raising public awareness of AMR, and gaining funding for research and surveillance. However, results from the commissioned literature review demonstrated the paucity and weakness of the evidence-base on parameters to assess the AMR BOD (Table 1). Following the presentation of these results during the expert consultation meeting, participants recommended the development of prospective studies to collect robust data to generate representative estimates of the burden of AMR, with a specific focus on blood stream infections as a proxy syndrome.

Table 1 Variables included in the GBD - DALY calculation

Variables	Methods	Sources
Incidence and/or prevalence	Surveillance Prospective studies	Enhanced GLASS AMR burden estimation studies
AMR attributable mortality	Literature review Prospective studies	Limited data available AMR burden estimation studies
Health states – definition and durations	Literature review Prospective studies	Limited data available AMR burden estimation studies
Disability weights	Existing estimates for other infections	WHO GBD estimates / ECDC Burden of communicable diseases in Europe (BCoDE) database Institute for Health Metrics and Evaluation (IHME) GBD estimates ³

GLASS will now work with partners towards five main outputs:

1. Development and pilot testing of proof of concept (POC) protocols for data collection to gather required information for AMR burden estimation (January 2018 – March 2019);
2. Estimation of BOD estimates for the POC study and evaluation of the tested methodology (April 2019-June 2019);
3. Implementation of defined methodology at global scale (July 2019 – December 2020);
4. Estimation of the global burden of AMR (January 2021 – June 2021).

This work is expected to generate unprecedented robust estimates for the global AMR health impact, collected using a systematic and harmonised approach across countries. In addition, the development of

³ <http://ghdx.healthdata.org/record/global-burden-disease-study-2016-gbd-2016-disability-weights>

standardised methods for estimating AMR burden that can be adapted to a range of settings will allow for effective monitoring and evaluation of both approaches to data collection and the metrics generated.

Technical meeting

On 17-18 January 2018, the WHO organised an expert consultation meeting on AMR health burden estimation. The technical meeting included discussion of a focused literature review of current research designs for and challenges in the adequate data collection and assessment of the clinical and health AMR burden, and how the WHO can and should initiate more comprehensive data collection to develop robust BOD estimates for AMR. During the meeting, findings from the literature review were presented and discussed together with a number of expert presentations on related research by members of the committee. The analysis of strengths and weaknesses of collected evidence, and the feedback from experts will inform the development of a protocol for proof of concept epidemiological studies focused on estimating the burden of antibiotic resistant infections.

The meeting was composed of three sessions: I) Current and past history of burden calculation and health outcomes; II) Approaches and methods to estimate AMR health burden; III) Development of protocols and pilot studies for AMR burden estimation.

Key objectives of the meeting:

1. Discuss literature findings;
2. Assess proposed methodologies;
3. Discuss protocols for epidemiological studies aimed at capturing AMR burden;
4. Discuss protocols for data collection that will allow for the estimation of AMR burden and other parameters linked to it.

1. Presentation overviews

GLASS – Global AMR Surveillance System by Carmem Pessoa-Silva (WHO). GLASS is the first global system to collect official national data on AMR in eight selected bacterial pathogens causing common infections in humans. The aim of GLASS is to document the status of existing or newly developed national AMR surveillance systems to foster capacity building, and provide a standardised approach to the collection, analysis, and reporting of global data on AMR across countries. These aims will support the long term goal of collecting surveillance data needed to generate robust estimates of the AMR burden. Within GLASS, AMR data are collected through a case-reporting surveillance system, which collates test results for priority specimens from blood, urine, and stool, as well as cervical and urethral specimens routinely sent to laboratories for clinical purposes. GLASS is promoting a shift from surveillance approaches based solely on laboratory data (isolate-based data) to a system that includes epidemiological, clinical, and population-level data. This approach has been shown to strengthen understandings of the impact of AMR on human health, and enable better analysis and prediction of AMR trends.

Review on study designs and methodological challenges to monitor clinical burden of multiresistant bacteria – Limitations & potential avenues to follow by Evelina Tacconelli (Tubingen and Verona Universities). The review indicated that current estimates of the burden of AMR are very poor, and mainly rely on prevalence data from single centres, retrospective cohorts and case-control studies performed in high income countries (HICs) and assessing very limited health outcome measures. The definitions of outcomes vary substantially across studies, and the statistical methodology is often of poor quality. Mortality is most frequently reported as crude-mortality, and very few studies assesses the length of stay (LOS) after infections. Complications are reported usually only during hospitalisation and within a short follow up (not longer than 4 weeks). A limited number of studies focus on high risk populations (cancer, transplants, HIV). Only one third of the studies apply scores for the assessment of comorbidities. Sample size determination, or sensitivity and interaction analyses are also very rarely performed. Definition of controls is provided in a minority of the case-control studies, and among the matched studies less than half specified the analysis used to account for matching. The review highlighted the need to develop a standardised methodology for data collection on AMR epidemiological parameters based on the already established WHO GBD methodology, to inform the generation of required metrics. The development of this methodology will require: the provision of incidence (prevalence) and mortality data for health outcomes of interest; the prioritisation of infections based on their clinical impact; measurement of the duration and distribution of health states; and the design of specific outcome trees (models describing the disease progression pathway and linking the infection with possibly sequelae) for each clinical syndrome caused by resistant bacteria.

Global burden of drug resistant TB by Philippe Glaziou (WHO). The Global Project on anti-Tuberculosis (TB) Drug Resistance Surveillance (DRS) was initiated in 1994, with the aim of measuring the prevalence of anti-TB drug resistance worldwide through representative data on tested pulmonary cases with bacterial confirmation, disaggregation by treatment history, and quality assurance of drug susceptibility testing. Through national surveys and routine testing, the DRS programme measures resistance among new and retreated TB cases, including rifampicin resistance (RR), multidrug-resistant TB (MDR-TB) resistant to rifampicin + isoniazid, and extensively drug-resistant TB (XDR-TB) with additional resistance to any fluoroquinolone and at least one injectable second-line drug. In 2016, RR in new cases was 4.1% (2.8 - 5.3) and 19% (9.8 - 27) in retreated cases. There is no strong evidence of a global increase in MDR among TB in the past 10 years, or of increasing of global additional resistance to any fluoroquinolone and any injectable 2nd line drug.

PANORAMA project - short overview by Andrew Stewardson (The Alfred Hospital and Monash University and Geneva University Hospitals). The PANORAMA Project is a prospective cohort study to estimate the clinical impact of carbapenem resistance among patients with Enterobacteriaceae bloodstream infections in low- and middle-income countries. This study included 297 patients from 16 hospitals in 10 countries, and sought to use robust methods to account for the common challenges of misclassification bias, confounding, time-varying exposures, competing outcomes (in-hospital death and discharge alive) and missing data. Approaches to deal with these challenges included confirmatory microbiological testing at a central laboratory, use of a directed acyclic graph to be explicit about causal associations, inverse probability weighting to account for confounding in the context of relatively small numbers of outcomes, multiple imputation for missing data, and modelling of the effect of resistance on

both death and discharge alive (competing outcomes). It was proposed that the successful implementation of this project supports the feasibility of further prospective patient-level studies addressing AMR burden in LMICs. If we want to implement AMR BOD studies in LMICs, the most important thing to consider is the need for a simple minimum requirement list for data collection (exposure, outcomes, confounders), to which we can add a more extended (wish) list.

From AMR Surveillance to AMR Burden by Visanu Thamlikitkul (Mahidol University). The objective of the study was to determine feasibility and benefit of GLASS for surveillance of blood culture specimens. GLASS was implemented at Siriraj Hospital in Bangkok, Thailand using a locally developed web application program (app) to transfer blood culture specimen data, and to enter clinical data of patients with positive blood culture by infection control nurses and physicians via the app installed in their smart phones. In-hospital mortality was significantly higher in patients with antibiotic resistant bacteraemia than in patients with antibiotic non-resistant bacteraemia (40.5% vs. 28.5%, $p < 0.001$). The patients with antibiotic-resistant bacteraemia consumed more resources than those with antibiotic non-resistant bacteraemia. Blood culture results combined with patient clinical data were shown to have more benefit for surveillance of antimicrobial resistance, and to be more applicable for developing local antibiotic treatment guidelines for patients suspected of having bacteraemia. AMR burden of bacteraemia is estimated from the data from GLASS as follow: estimated annual number of true bacteraemia is 946 patients in which 419 of them are AMR bacteraemia; estimated annual number of deaths is 365 patients in which 194 of them are AMR bacteraemia; estimated total annual healthcare cost for bacteraemia patients is US\$ 10,854,132; cost of non-AMR bacteraemia per admission is US\$ 8,614 per admission compared with US\$ 15,379 per admission for AMR bacteraemia; cost of community-acquired bacteraemia is US\$ 4,725 per admission compared with US\$ 16,233 per admission for hospital-acquired bacteraemia; and estimated DALY per year of all bacteraemia is 6,034 DALYs in which DALY of AMR bacteraemia is 3,190 DALYs.

Simulation models for burden estimation by Niel Hens (University of Antwerp). The purpose of mathematical models is to predict and investigate the factors that drive dynamics. Building a model presents a trade-off between accuracy, transparency and flexibility. Models present a simplification of reality and chance events of infectious disease transmission hinder perfect prediction. A good model is suited to its purpose, balances accuracy, transparency, flexibility and it is parametrisable from available data or can show us which data needs to be collected by conducting sensitivity analyses. Statistical and mathematical models should be used together as they are complementary of each other and would converge towards the same results – the *a posteriori* and the *a priori* methods. Modelling issues are generally associated with incomplete data, identifiability or biological plausibility. For these reasons mathematical and statistical models, if properly used, offer valuable instruments to understand mechanisms of antibiotic use and resistance taking into account the different sources of uncertainty. As the amount of data that is being collected through different systems increases, using different data streams together would provide a useful tool to improve burden estimation. How these data should be combined includes understanding any potential bias that might arise from the different data sources and the development of new methodology which is part of what is now being framed as data science.

Burden estimates from DRIVE-AB and using the HECTOR methodology to supplement them by Yehuda Carmeli (Tel Aviv University). The aim of the project was to measure the prevalence of *Escherichia coli* and *Klebsiella pneumoniae* infections resistant to third generation cephalosporin and carbapenems in a number of countries. The hypothesis was that the number of susceptible *E. coli* and *K. pneumoniae* infections would be the same across countries. Point prevalence was generated together with confidence intervals. The research used an additive model in which resistant infections supplemented susceptible infections, rather than replacing them, as otherwise countries with more resistance would have lower numbers of susceptible infections. Ascertainment bias was another important factor to consider in relation to data collection on the frequency of drug-resistant infections across countries, especially for LMICs. There were also challenges in obtaining data on community infections, however for infections requiring IV therapy it was assumed that all patients would be hospitalised, though this could differ in settings with less access to healthcare.

The objective of the HECTOR project (developed and rejected in 2007/2008) was to combine incidence data coming from different AMR surveillance systems by acquiring denominator data, and embed that in nested studies of outcomes in order to generate burden of resistance estimates. Using the tools developed, countries could do their own analysis and contribute the generated information to a global open repository. The aim was to create global expertise by recruiting a number of AMR outcome experts and to provide necessary coordination in order to enable participating partners to estimate impact of AMR, both on patients' health and costs for healthcare systems.

Monitoring and mapping the global burden of antimicrobial resistance: Building on GBD leadership and research by Andy Stergachis (IHME, University of Washington). The Global Burden of Disease, Injuries, and Risk Factors Study (GBD) Study is an ongoing comprehensive global research program that provides comparable estimates of mortality and disability resulting from 328 disease and injury causes, as well as from 84 risk factors, across age and sex groups over time and space. The established infrastructure of the GBD attracts over 3,100 collaborators in 140 countries and 3 non-sovereign locations around the world. GBD has the largest known existing repository of epidemiological data; this data is used to compare the loss of healthy life due to a particular health disparity around the world relative to other causes of disability and mortality. A new initiative between IHME and Oxford University's Big Data Institute (BDI) has been created to provide quantitative evidence on the burden of disease arising from AMR, and how it is changing, in order to increase global awareness of AMR, and to support global efforts to control it. Supported through a number of separate, but complimentary streams of work, this initiative combines IHME's considerable strengths in disease burden estimation and geostatistical modelling with the BDI's unique knowledge of AMR, access to in-country data, and parallel expertise in high-resolution mapping of disease outcomes. Its goal is to inform decision-makers at every level (local, regional, national and global) with the best available evidence on levels, trends and drivers of health so that decisions are ultimately more evidence-based. It will also provide free, public access to study results through interactive data visualizations. The AMR work currently underway includes GBD for sepsis and it aims to provide data-driven estimates of sepsis incidence, prevalence, morbidity, and mortality, stratified by age group, sex, year, location, and primary cause of death, and the specific contribution of AMR

2. Topic specific discussions

A. Approaches and methods to estimate AMR health burden: context & targets

The objectives of GLASS AMR burden estimation studies, and criteria to apply when generating data (e.g. representativeness, feasibility and cost) were discussed. A number of approaches were considered, and the identification of a health condition of interest and target populations was deemed a good starting point. The experts agreed that the same metric (DALYs) used by the WHO to estimate the Global Burden of Disease (GBD) could be a good means of estimating AMR burden. In this context, a robust approach to data collection is essential to measure AMR epidemiological variables and generate knowledge on AMR health impact, together with the development of a consistent methodology that can be tracked and monitored globally. The data entry point for generated information will be GLASS, to guarantee government ownership of the data and the standardisation of data collection and reporting.

In principle, for disease burden estimates already produced by the WHO, the fraction of morbidity or mortality associated with resistance, and therefore its burden, should be calculated. In this regard, the GBD methodology enables attributable risk to be calculated to quantify the contribution of AMR to a condition or death, as well as how much lower the burden of disease would be if the population had not been exposed to that specific risk factor (population attributable risk). The difference is the attributable burden. However, AMR brings an extra level of complexity. If infections by resistant pathogens are prevented, this could result in: a) absolute reduction in the number of infections equal to the frequency of resistant infections (additive scenario); b) no reduction at all if patients are now infected by the susceptible counterpart (replacement scenario); c) part reduction due to a mixed scenario. Thus, reduction of resistant infections does not linearly translate in the reduction of the same proportion of related mortality, as a patient could still die by the same infection caused by a susceptible strain of the pathogen. In other words, it is possible to measure, in a set period of time, how many patients who died were infected by a resistant pathogen, but it is not possible to measure how many patients with a resistant infection have died because of it, as AMR can only be an underlying cause of death. Moreover, when looking at attributable mortality or frequency of disease for complex conditions (e.g. diarrhoea in children), it is often very difficult to identify a single causative agent; the same principle applies for resistant pathogens. In a number of cases, diagnostics will not have been carried out, and the causative agent will therefore be unknown, resulting in ascertainment bias. Nevertheless, it is believed that resistance causes excess mortality and morbidity – though quantification of this is difficult. All these factors have to be taken into consideration when identifying a protocol for AMR burden estimation.

To address some of these issues, the aim for the first phase of GLASS work on AMR burden is to develop and pilot proof of concept (POC) studies for estimating the health impact of AMR. These studies can serve to test selected methodologies in a number of countries, and produce baseline information for the development of approaches that can then be scaled up to the global level and integrated within the GLASS framework. GLASS is currently helping to build the necessary national infrastructure to allow for the collection of more reliable and comprehensive AMR data. Enrolled countries are aware that variables collected by typical AMR surveillance systems are not sufficient to provide estimates for burden, and are keen to participate in new initiatives.

Based on the current GLASS reporting structure, it was determined that the first phase of this work would focus on bloodstream infections (BSIs) for AMR burden estimation. As the pathogens GLASS monitors in blood specimens are very rarely contaminants, positive blood cultures should provide more reliable results for frequency of bloodstream infections than, for example, positive urine cultures for frequency of urinary tract infections. Models can be built to identify the indicators needed to calculate the burden of disease for susceptible and non-susceptible bloodstream infections, and guide data collection under the GLASS umbrella. Whilst the focus on bloodstream infections could initially lead to underestimates of the burden of AMR, the long-term goal is to enhance the GLASS system based on the tested methodology, in order to collect more diverse, reliable and comprehensive estimates in the future.

B. Approaches and methods to estimate AMR health burden: what we need

As per WHO GBD methodology, the disability-adjusted life-year (DALY) was chosen as a single measure to quantify the health impact of AMR and associated risk factors. DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population, and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences. Producing meaningful DALYs for BSIs due to resistant pathogens might not be possible in this first phase, but intermediate steps will be taken to generate variables needed for the calculations, including incidence/prevalence, mortality, BSI characteristics and duration of sequelae of BSIs due to resistant pathogens.

AMR attributable mortality is preferred over crude-mortality, to avoid overestimating the impact of AMR by including mortality related to underlying illnesses. Although surveillance data are very often not detailed enough to estimate attributable mortality, focused studies allow for its estimation through analyses adjusted for confounders, and knowledge gaps can be filled using mathematical models. Given that AMR is not a disease, and can only be considered as an underlying cause of death, the multiple cause of death (MCD) framework can be used to inform the measurement of AMR attributable mortality, either to correctly assess and categorise causes of mortality, or examine the combination of multiple causes of death.

BSIs are acute infections, and incidence is utilised instead of prevalence as the parameter of interest, as prevalence will result in an underestimation of the true burden. In order to calculate incidence, a population denominator has to be estimated, such as health facility catchment areas, or preferably number of patient days or admissions. A number of options for denominator estimates are available for hospital acquired infections (HAI) (e.g. incidence per 1000 patient days in a given hospital), while for community acquired infection (CAI), the denominator is more difficult to determine, which requires further consideration. Additionally, incidence of acute infections in LMICs can be heavily underestimated, as access to healthcare facilities (HCFs), diagnosis, and treatment may be limited.

All possible sequelae, disabilities, and complications associated with BSIs will have to be identified and monitored to inform the health states and disability weights for DALY calculations. Definitions of health states should not change in relation to the economic status of countries. Disability weights reflect the

severity of the disease and its sequelae on a scale from 0 (perfect health) to 1 (equivalent to death). Years Lost due to Disability (YLD) are calculated by multiplying the incident cases by duration and disability weight for the condition. Although collecting these data might prove to be very complex, and some of these factors might not contribute to the burden of bloodstream infection as much as mortality, evidence is still needed to measure the magnitude of their impact. Dialysis, amputation, paralysis, and sepsis are all possible bloodstream infection sequelae that could heavily impact on DALYs based on their related disability weights. For most health outcomes associated with AMR, disability weights have not yet been estimated. It will have to be established whether the sequelae of resistant and susceptible infections are different in nature, or whether they are similar but occur with different frequency, intensity or duration, and subsequently require different disability weights.

Finally, data have to be collected for covariates and confounders. The initial aim is to collect data on a wide range of factors, and use mathematical and statistical methods to define which variables have a large effect on possible outcomes and should be included in future surveillance. An essential list could then be compiled based on the minimum necessary information required to generate reliable estimates, which could be extended to a larger list for centres with easier access to data.

C. Approaches and methods to estimate AMR health burden: explore potential approaches for pilot studies and identify strengths and limitations

Among possible approaches, a HCFs cohort study design, which allows stratification of infection origin (hospital vs community), was suggested for the collection of AMR epidemiological variables. Patients with fever and a number of predefined clinical signs, or those with blood tests, would be considered for inclusion in the study. Control patients would consist of patients with susceptible infections, and uninfected patients (e.g. no positive BSI culture and without chills).

Although a syndrome-based approach allows for better representativeness than a diagnostic-based approach, especially in settings with limited diagnostic services, it can be quite laborious to implement, and might not be the most cost- or time-effective method. However, in countries where very few positive blood samples are recorded, syndromic approaches might help minimise the distortion generated by diagnostic results, which often are representative of patients with severe cases for whom a number of treatment options have already failed. These factors have to be taken into consideration when choosing the most appropriate design.

Given the risk of ascertainment bias, particularly in low-income countries (LICs), parallel studies should be designed to estimate the proportion of the population that cannot be captured by diagnostic-based surveys. It is important to note that, even if the level of underreporting could be estimated, the measurement of variables needed (attributable mortality, incidence and health states duration) will be possible only for patients who are symptomatic, can access HCFs and are blood-tested. Nevertheless, these are also the patients who would benefit from better treatment options.

A careful decision must be made when choosing between quality and representativeness of the data collected. The selection of HCFs for study recruitment depends on the variables to be collected. For example, to best capture attributable mortality, it could be better to draw a sample from highly

functional and organised hospitals, as it is more feasible to accurately follow up patients and monitor comorbidity or other possible causes of death. On the other hand, to generate prevalence and incidence data, a more representative sample of the target population is needed, and a large HCF from a less well-resourced setting, although not as functional, might be more appropriate. A country's economic status and healthcare system structure are also important factors to consider. Patients with bloodstream infections are more likely to be identified by hospital-based surveys in high-income countries (HICs), and the results are often a good representation of the event in the overall population. However, mortality and resistance rates in such settings may not be accurate representations, as these facilities might also have better management, resources, or treatment practices. For example, access to effective antibiotic therapy strongly affects mortality rates in resistant patients who are more likely to be treated with better drugs. It has also been shown that high resistance rates are often found in HCFs with poor infection control and poor academic establishment. These limitations have to be acknowledged when choosing the study area and the target facility.

D. Development of protocols and pilot studies for AMR burden estimation: how to do it

Several approaches were suggested by meeting participants for future explorations. A combination of approaches will probably be needed to complement and adjust the data collection of AMR epidemiological variables in different settings, and allow for a better understanding of the context in which the studies are run and the level of potential bias generated.

When selecting facilities for the studies, two options can be considered: 1) Very functional HCFs in HICs can be prioritised to allow for the collection of a broad number of variables and high quality data. Models can then be utilised to define the best approach and data needed to generate the same estimates in LMICs. 2) Studies can be piloted in a number of countries at different levels of economic development, choosing facilities with similar characteristics to compare outputs and evaluate whether the chosen methodology fits diverse settings. HCFs can be classified based on function or location (e.g. district, provincial or central hospitals; primary or secondary HCFs; tertiary care university hospitals; community HCFs, etc.). Ethical approval will be required for data collection of individual patient characteristics based on the requirements of each chosen facility.

The selection of pathogens to monitor should be informed by the epidemiology of the area of study and the chosen outcome tree. Information will be generated both from collected data and data available in literature, and it is essential to be aware that including a high number of pathogens might add excessive complexity.

Mortality could be monitored at least at 14 days (and perhaps 30 days) from the onset of the disease, to allow for more comparable measures than in-hospital mortality. If sites can generate one-year mortality data, this information could be used to evaluate the proportion of mortality associated with an acute event after a 6 month or a 1 year period, and whether these variables are needed to inform the models.

The first step in defining BSI health states will be to develop an outcome tree, list parameters needed to develop the database, and circulate it to experts for them to select health states that are most critical to burden estimation. Simulations can then help identify which parameters most impact the models, and

examples of burden calculations (e.g. for other acute infections such as malaria, or non-infection conditions such as ruptured aortic aneurysm) can help define what information to include. Long-term follow up might also be necessary to monitor sequelae in patients, and chose which to include in the models. Case series studies can be set up to measure one-time events with appropriate statistical methods, and results can be used to inform health states parameters.

Patient demographics and clinical history, co-morbidities, severity of illness at the time of bacteraemia onset and before treatment initiation, and duration of illness are some examples of covariates and confounders that could be collected. Comorbidities could be added as covariates in models, or evaluated by a scoring system, for which different methods were discussed during the meeting. Confounders present before the onset of the bloodstream infection will have to be identified and separated from the ones that are on the casual pathway of the infection to mortality.

To control for selection bias, surveys could be designed and implemented to evaluate health care seeking behaviour in the catchment areas for selected HCFs, or more broadly, for the target population. Blood-testing practices could also be monitored in those facilities. For example, ad-hoc studies can be run to measure how many patients are diagnosed with fever and how many blood cultures are performed during a set time period, or to monitor how many patients under antibiotic therapy have blood samples taken. This information can be used to generate corrective factors for further analysis.

Finally, characteristics of selected facilities could be recorded together with indicators on epidemiological variables, microbiology capacity and quality assurance, both for bacterial identification and antibiotic susceptibility testing (AST).

Steps forward and further research

- GLASS AMR burden estimation methodology will be developed in line with the WHO BOD methodology.
- A syndrome-based outcome tree will be designed to identify indicators and health states to be measured (sequelae) per pathogen. Discussion is still open on how to approach the measurement of disability weights for the calculations of DALYs, and whether specific weights need to be estimated for sequelae related to resistant pathogens.
- Initially, GLASS will run prospective proof of concept (POC) studies in different settings, including LMICs, HICs, tertiary care hospitals, and community health centers, to test the selected methodology. POC studies will focus on bloodstream infections caused by pathogens currently included in GLASS. At this stage, there will be no attempt to generate global AMR burden estimates.
- A potential design to be tested could be an HCFs-based cohort study, including both community- and hospital-acquired infections, whereby controls would consist of patients with susceptible infections, and uninfected patients (no positive BSI culture and without chills). For community patients, community mortality rates could be used.
- Parallel studies (e.g. inventory/capture-recapture studies/Knowledge Attitude Practices studies) should be run to estimate under-diagnosis and to collect data on health care seeking behaviour within the target population.

- Once tested and refined, the methodology, representativeness of data, feasibility and cost will be evaluated, and the approach will be refined for inclusion in the GLASS framework. Country-level analysis can follow to estimate how well the methodology scales to broader settings.

With the support of partners, GLASS will design a protocol for prospective studies aimed at measuring the incidence of antimicrobial resistant infections, attributable mortality and the length of associated health states. Previous studies (e.g. PANORAMA), literature reviews and mathematical models can be used to assist in the design of prospective studies, and the parallel studies needed to assess detection bias and representativeness of collected data. The protocol will be tested in different settings, followed by monitoring and evaluation. The methodology will be adapted to be used across settings globally, and included in the GLASS framework. Population metrics and case detection rates will be generated and AMR DALYs estimated.

**WHO Expert Consultation meeting on Antimicrobial
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