

MEETING ON GLOBAL SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN INVASIVE CANDIDA INFECTIONS

24 APRIL 2018, MADRID, SPAIN

Organization of the meeting

Technical chair: Dr Jacques Meis (Netherlands)

Co-chair: Dr Carmem Pessoa-Silva (Switzerland)

Participants

In addition to the co-chairs, 24 participants were present. The full details of meeting participants can be found in Annex 1.

Dr Ana Alastruey-Izquierdo (Spain)
Dr Hanan Balkhy (Saudi Arabia)
Dr Nienke Bruinsma (USA)
Dr Arunaloake Chakrabarti (India)
Dr Leili Chamani-Tabriz (United Arab Emirates)
Dr Methee Chayakulkeeree (Thailand)
Dr Tom Chiller (USA)
Dr Arnaldo Colombo (Brazil)
Dr Susana Cordoba (Argentina)
Dr Oliver Cornely (Germany)
Dr Sergey Eremin (Switzerland)
Dr Joveria Farooqi (Pakistan)
Ms Kaitlin Forsberg (USA)
Dr Nathalie Friberg (Finland)
Professor Nelesh Govender (South Africa)
Dr Thi Hoa Nguyen (Vietnam)
Dr Elizabeth Johnson (United Kingdom)
Dr Katherine Kooij (The Netherlands)
Dr Cornelia Lass-Flörl (Austria)
Professor Olga Perovic (South Africa)
Dr Diamantis Plachouras (Sweden)
Dr Aparna Singh Shah (India)
Dr Jong-Hee Shin (Korea)
Dr Susana Zurita (Peru)

Rapporteur

Dr Laura Nellums (United Kingdom)

Welcome remarks and introductions

Speaker: Dr Pessoa-Silva

Objectives achieved: Introductions and context

Reference document: PowerPoint, Annex 3

Following introductions, Dr Pessoa-Silva thanked participants for their attendance, and framed the meeting in relation to increasing concerns around antimicrobial resistance (AMR) in fungal infections, and invasive *Candida* infections specifically. Dr Pessoa-Silva outlined the meeting objectives, including: 1) informing the development of the framework for AMR surveillance in candidemia; 2) defining the criteria for sentinel sites for piloting the framework; and 3) initiating a global invasive fungal infections AMR network.

Background on WHO Global AMR Surveillance System (GLASS)

Speaker: Dr Eremin

Objectives achieved: Common understanding of GLASS objectives and its current phase

Reference documents: PowerPoint, Annex 3; GLASS manual¹

Dr Eremin described lessons from the 2014 Global Report on AMR Surveillance,² highlighting limitations in existing surveillance and knowledge of AMR and its impact on humans. He described the development and purpose of GLASS, the first global system to collect official national data on AMR in selected bacterial pathogens, which is in the early implementation stage. Dr Eremin provided an update on current priority pathogens, surveillance approaches used, the status of countries enrolled, and results from the first GLASS report,³ as well as information on GLASS data on the web,⁴ the Emerging AMR Reporting (EAR) module, One Health AMR surveillance, and monitoring of antimicrobial consumption. In the following discussion, Dr Pessoa-Silva described the involvement of Member States in informing the development of the framework, and Dr Eremin emphasized the importance of capacity building as part of GLASS.

Framework for AMR surveillance in fungal infections in GLASS

Speaker: Dr Chiller

Objective achieved: Discussion of the draft framework for global surveillance of invasive fungal infections

Reference documents: PowerPoint, Annex 3; draft framework, Annex 2

Dr Chiller began by providing a historical perspective of the report, beginning when CDC and others in the fungal community contributed to the fungal infection chapter in the 2014 WHO report on AMR surveillance,² and began discussing opportunities to form a network around surveillance of AMR in *Candida* infections. Dr Chiller reported on the growing concern around *Candida auris* to the GLASS collaborative platform, following which a working group was formed to discuss the inclusion of fungal infections in GLASS. A key objective of this meeting is to form a network and discuss challenges in harmonizing approaches to AMR surveillance in *Candida* species.

Dr Chiller described the challenges involved in fitting fungi into the existing framework, as many countries have limited capabilities for fungal surveillance. He highlighted the importance of starting small and simply, and structuring the framework to reflect GLASS methodology so that it can be seamlessly integrated. Participants discussed key questions for the development of the framework, including pathogen and specimen types, inclusion of selected sites versus national coverage, hospital versus community

¹ <http://www.who.int/antimicrobial-resistance/publications/surveillance-system-manual/en/>

² <http://www.who.int/antimicrobial-resistance/publications/surveillancereport/en/>

³ <http://www.who.int/glass/resources/publications/early-implementation-report/en/>

⁴ <http://www.who.int/glass/en/>

populations and specific focus on high risk patients, the need to collect both numerator and denominator data, and approaches to susceptibility testing.

Methodology: Epidemiology

Moderator: Dr Bruinsma

Objectives achieved: Epidemiological approach for the pilot phase discussed and agreed

Reference documents: PowerPoint, Annex 3; draft framework, Annex 2

The discussion focused on Chapter 2 of the GLASS *Candida* Draft Framework: GLASS *Candida* surveillance methods [Annex 2].

Framework section 2.1 Priority pathogen for surveillance: Candida spp.

Participants discussed what the priority pathogen for surveillance should be, particularly given the current emphasis of GLASS on antibacterial resistance, and the practicalities around surveillance coming from clinical settings. Participants also discussed challenges relating to heterogeneity in capacity, identification methods, susceptibility testing, and guidelines used for the classification of antimicrobial susceptibility testing (AST) results across countries and potential surveillance sites. It was determined that it would be more strategic to start small, with the option of expanding the focus over time. Dr Pessoa-Silva noted that developing the scope of surveillance in a step-wise manner was raised through consultation with Member States. Dr Eremin also reminded participants that GLASS EAR was specifically designed to accommodate rare species or emerging resistance. Participants selected blood as a priority specimen, and *Candida* spp. as the priority pathogen for the pilot. It was also decided that participating clinical sites or sentinel centers would be required to report both AST interpretation results (e.g. resistant, intermediate, susceptible [RIS] where breakpoints are defined) and minimal inhibitory concentrations (MICs) (with the provision that for those sites that would otherwise be able to contribute to the pilot, it may be feasible for them to send samples to technical partners to obtain MIC data). During the development of the protocol, this will be further discussed and defined.

Framework section 2.2 Specific patient populations: high risk patients

It was decided that the pilot would include surveillance sites serving at least one or more high risk patient groups (e.g. intensive care, neonatal, transplant, hematology, oncology, or other high dependency units). Surveillance data would include positive and negative blood cultures (one sample representing one patient, with data being de-duplicated for multiple patient samples), so both numerators and denominators are reported. Clear definitions on the way to report the total number of blood cultures will be described in the protocol. Participants also discussed challenges around de-duplicating data such as multiple blood cultures, which may be taken for a single patient for different purposes, and other options for denominator data were suggested such as patient admissions or patient days. The standard for data collection was discussed, including the need for isolate/patient-level data collection, as well as which variables (e.g. facility, department) should be included in addition to the already existing GLASS variables. During the development of the protocol, this will be further discussed and defined.

Methodology: Laboratory

Moderators: Dr Chakrabarti, Dr Chiller

Objective achieved: Agreed laboratory approach for pilot phase

Reference documents: PowerPoint, Annex 3; Draft framework, Annex 2

Framework section 2.7 Participation

Dr Chakrabarti presented PowerPoint slides [Annex 3] outlining National Reference Laboratories (NRLs) and National Coordinating Centers (NCCs) (aligning with definitions in GLASS), as well as *Candida*

Reference Centers (CRCs)⁵ and surveillance sites. This was followed by discussion about identification methods and potential challenges across countries, with concern about a lack of standardization across sites, and that numerous laboratories may only be able to specify specimens as *Candida albicans* or non-*albicans* yeast. Participants also discussed the number of antifungals to include in the pilot, electing to initially focus on fluconazole and echinocandins. The key objectives of the project were also discussed, with reference to whether aims should be to demonstrate the impact of resistance on human populations, show what is happening among patients in hospitals or at the country level (requiring representative data), or identify capacity and priorities across countries. Dr Pessoa-Silva emphasized that the function of this pilot is to inform a framework to propose to countries. She also highlighted the need to be able to identify the relationship between susceptibility testing producing MIC and other (e.g. RIS) results.

Data validation and analysis

Moderator: Dr Eremin

Objectives achieved: Approach to validation and epidemiological output agreed

Reference documents: PowerPoint, Annex 3; Draft framework, Annex 2

Dr Eremin began by showing the schematics of GLASS data flow, illustrating the pathway from microbiological/clinical data at surveillance level, to national data management, to global data management (GLASS), which is also needed for fungi. Dr Eremin also described WHONET, which was developed to support AMR surveillance and has been adapted for GLASS. The software is capable of generating aggregated data in the format accepted by the GLASS IT platform, facilitating participation for countries with more limited capacity for data management. Two options exist for submitting data to GLASS: file upload (for aggregated data or individual data) or direct entry (individual data). Participants discussed their experiences of submitting data to the system, and specific data management issues (e.g. anonymization of individual data, de-duplication).

Standard operating procedures and capacity building

Moderators: Dr Chakrabarti, Dr Chiller

Objectives achieved: Agreed approach for standard operating procedures, and addressing capacity building and disparities in baseline fungal diagnostic capacities across countries

Reference documents: PowerPoint, Annex 3; Draft framework, Annex 2

Detailed standard operating procedures (SOPs) are in place for antibacterial resistance. For fungi, similar procedures will be agreed for sample collection, transport and processing, identification, susceptibility testing, and External Quality Assurance System (EQAS). Dr Pessoa-Silva noted that currently WHO does not have specific laboratory guidance on mycology methods for identification and antimicrobial susceptibility testing in *Candida* spp. The pilot could use existing agreed international standards, and the need for the development of a WHO guidance document should be assessed. The agreed approach was to initially build on existing international standards, from which laboratories would develop SOPs.

Dr Chakrabarti presented a survey of laboratory practices for diagnosis of fungal infection in seven Asian countries (Chindamporn et al *Med Mycol* 2017, Sep 20; Annex 5). He then discussed capacity building, outlining three tiers: 1) countries with developed laboratories; 2) countries with limited laboratories; and 3) countries with no/very minimal laboratories. Required steps for each of these country classifications are outlined in the draft framework and the PowerPoint slides. Dr Chiller described the benefit of a pilot for identifying areas for capacity building, as well as where competing priorities may exist. The biggest

⁵ Proposed addition to the core components of a national AMR surveillance system defined in the GLASS Manual

challenge will be how to find resources to enable capacity building, which will include the technical expertise of meeting participants. Dr Bruinsma described the need to understand country-specific contexts in order to provide the right support. Dr Pessoa-Silva highlighted that this pilot will take advantage of a window of opportunity created by rising interest in AMR, and the momentum around developing action plans, surveillance, and allocation of resources.

Dr Chakrabarti noted that advocacy work may be useful for supporting capacity development, pointing to ongoing work around AMR in fungal infections in other institutions. Dr Pessoa-Silva described the need to see how such efforts can be combined and become sustainable, and to focus on capacity building in countries with limited or minimal laboratory capacity and how to embed this in national programs. In agreement with Dr Chiller, she emphasized that the pilot phase offers the opportunity to show the need for fungal infection diagnostics and susceptibility testing in high risk patients. She shared that this program needs to be strategically linked to other major agendas beyond AMR, such as for universal health coverage, and the sustainable development goals. This pilot is an opportunity to demonstrate that such surveillance is possible, and to generate standardized tools and guidelines so that this program can be implemented globally. In order to successfully do this, she argued for focusing on the first two tiers of countries in the pilot. Dr Chiller reiterated the important function of the pilot for basic capacity building and awareness raising to bring people together and initiate the first steps.

Dr Pessoa-Silva indicated the pilot phase should include at least one center in each of the six WHO Regions, and that whilst meeting participants can help to identify centers across the regions, there is also a need for a formal country approach, targeting centers strategically across the regions through engagement with WHO Regional and Country offices.

Pilot testing approach and time frame

Moderators: Dr Chakrabarti, Dr Chiller

Objectives achieved: Pilot testing plan discussed and agreed

Reference Documents: PowerPoint, Annex 3; Draft framework, Annex 2

Dr Chiller outlined sample steps [PowerPoint, Annex 3], including engagement of laboratories for pilot testing, data submission, validation, and evaluation. Dr Pessoa-Silva outlined the key phases that need to be achieved, including building the pilot and defining the final protocol, establishing support between clinical and reference laboratories, building capacity in each country, finalizing minimum requirements for reference laboratories (including whether meeting participants have capacity to provide support to reference laboratories), determining tools for species identification and susceptibility testing, and finally, development and testing of an IT module. She envisions the protocol will be finalized in July, and that these key steps will realistically be completed at the end of 2018 or early 2019, depending on availability of funds. Over the following year, the plan will be to carry out the pilot, collect data, and generate the final results. Dr Eremin agreed that the pilot is unlikely to occur before next year, and was originally proposed to coincide with the 2019 GLASS data call (planned for May – July 2019). Both he and Dr Chiller highlighted that the process will take time and effort, and whilst it can be phased and some components can be developed in parallel, there are numerous options that need to be considered in relation to data collection and analysis, defining variables for the dataset, and data submission and the platform through which this is done.

Dr Pessoa-Silva described that the overarching purpose is to test a framework that can be scaled up, though there will hopefully be secondary benefits such as awareness raising and capacity building. In order to facilitate the pilot, Dr Pessoa-Silva also outlined that it will be important to know about capacity and willingness of partner institutions to provide technical support. Dr Chiller suggested creating a spreadsheet,

as was done for GLASS, so that participants can indicate areas in which they can provide technical support. The discussion concluded with agreement around finalizing the protocol as soon as possible (July), at which point it will be feasible to engage in dialogue with and formally invite countries for the pilot phase.

Ways to work together: Pilot sites, working groups, and timeline

Moderators: Dr Bruinsma, Dr Pessoa-Silva

Objectives achieved: Discussion of roles and responsibilities; work plan 2018-2019 for development of AMR fungal module in GLASS

Dr Pessoa-Silva acknowledged the five collaborating centers present at the meeting, as well as the other technical partners, who were identified because of their expertise and capacities to contribute to this work, as well as the role they can have as advocates for the program. In order to establish roles/contributions of technical partners, a matrix of activities and support will be circulated following the meeting.

In the following discussion about engaging regional offices and follow up from the meeting, Dr Pessoa-Silva reiterated that a meeting was held in March with all regional offices and collaborating centers supporting GLASS, during which fungal surveillance was specifically discussed. Participants offered suggestions for other ways to ensure awareness about this program, for example putting information about the pilot on the GLASS website.

Participants were reminded of the SharePoint site set up for internal communications, through which all documents will be circulated. The tentative timeline was then presented.

• Publish meeting report	July 2018
• Finalize protocol	July 2018
• Start communication with countries through WHO Regional Offices	August-November 2018
• Develop and pilot tool for assessment of laboratory capacity for identification and susceptibility testing of candidemia	September 2018
• Define sentinel sites at country level	November-December 2018
• Develop IT tools for data entry and submission to GLASS	December 2018
• Pilot test the framework	January–June 2019
• Summarize and publish the pilot results	November-December 2019
• Revise and finalize the framework for AMR surveillance in candidemia based on pilot testing	December 2019

Participants discussed what year to select for surveillance data, and that it may be of benefit to have retrospective data included in the pilot in order to adhere to the timeline and receive sufficient testing data. Dr Pessoa-Silva also raised the possibility of developing an assessment tool to be shared with surveillance sites to assess practice and capacity, suggesting this is developed and submitted to sites prior to the pilot to identify who may be able to be included. She also acknowledged that this is an ambitious project, and that the timeline discussed represents what is ideally desired. The project will be facilitated by the matrix of tasks and participation, and partners will be asked to contribute at different stages. In addition to frequent communication of progress, there may also be another meeting towards the second part of next year.

Next steps and closing remarks

Speaker: Dr Pessoa-Silva

Objective achieved: Clarity on next steps

Participants again discussed that a key next step is to identify sites across countries. Dr Farooqi gave the example of her own institution, as they have capacity to be the national center for *Candida*, but that she is concerned they may not be the main coordinating center, and that financial support will be required. Participants discussed the potential need for technical partners to provide support with MIC testing, which shall be one of the key tasks in the matrix of work, and Dr Chiller reiterated MIC testing can be supported by CDC where feasible.

Dr Pessoa-Silva concluded the meeting by thanking the participants, the two WHO Collaborating Centres leading the technical support to this initiative (IND-99, Dr Chakrabarti, and USA-417, Dr Chiller), and Dr Meis (Chair). She emphasized that this work is likely to require 4-5 years, and that the commitment of technical partners to the key tasks in the matrix of work will be essential, but that she feels it is achievable if everyone's expertise is brought together, and if the ideas and project are kept grounded and realistic.