



# **Report of the 2nd Meeting of the Global AMR Surveillance System (GLASS) Collaborative Platform**

15-16 December 2016

Kempinski Hotel

Geneva, Switzerland

## **Meeting Report**



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## Abbreviations

AFR	antifungal resistance
AFST	antifungal susceptibility testing
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	antimicrobial resistance
AST	antibacterial susceptibility testing
BSI	bloodstream infection
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CC	Collaborating Centre
CDC	US Centers for Disease Control and Prevention
CIA	critically important antimicrobials
CLSI	Clinical and Laboratory Standards Institute
CPG	clinical practice guideline
CRE	carbapenem-resistant <i>Enterobacteriaceae</i>
DRC	Democratic Republic of the Congo
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease prevention and Control
EGASP	Enhanced Gonococcal Antimicrobial Surveillance Programme
EQA	external quality assessment
ESBL	extended-spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization of the United Nations
FIND	Foundation for Innovative New Diagnostics

GASP	Gonococcal Antimicrobial Surveillance Programme
GLASS	Global Antimicrobial Resistance Surveillance System
GFN	WHO Global Foodborne Disease Network
ICU	intensive care unit
LSHTM	London School of Hygiene and Tropical Medicine
MIC	minimum inhibitory concentration
MM	molecular methods
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NAAT	nucleic acid amplification test
NAP	national action plan
NGO	nongovernment organization
NRL	national reference laboratory
OIE	World Organisation for Animal Health
PCR	polymerase chain reaction
POC	point-of-care
PPS	point prevalence study
ReLAVRA	Latin American Antimicrobial Resistance Surveillance Network
STI	sexually transmitted infection
TB	tuberculosis
TOR	terms of reference
TP	target product
TPP	target product profile
WGS	whole genome sequencing
WHA	World Health Assembly
WHO	World Health Organization



## Summary Report

### Introduction

On 15-16 December 2016 WHO hosted a meeting with WHO Collaborating Centres, partner technical institutions and international AMR surveillance networks on the implementation of the WHO global antimicrobial resistance surveillance system (GLASS). The purpose of the meeting was to support development, dissemination and implementation of global AMR surveillance. Expected outputs from the meeting were:

- A common understanding of the status of GLASS development and support to global AMR surveillance efforts
- Defined next steps to address some AMR surveillance challenges:
  - i. AMR in invasive fungi
  - ii. Detection of emerging colistin resistance in *Enterobacteriaceae* and application of molecular methods for AMR surveillance
  - iii. Rapid alert component for emerging/new types of AMR within GLASS

### 1. Global surveillance of AMR and antimicrobial use: an update from WHO and partners

During Session One, participants were updated on the following:

#### 1.1. Overview of GLASS and update on early implementation.

GLASS is on track with its early implementation road map. By December 2016, 38 countries have expressed interest in enrolling in GLASS and 29 have completed procedures for enrolment. Next steps include:

- Development of a rapid detection and alert framework
- 2<sup>nd</sup> Member States consultation, April 2017 in Sweden.
- Explore and start planning on: (i) AMR surveillance in invasive fungal infections and (ii) the application of molecular methods for AMR surveillance
- Create new modules in the GLASS IT platform for ESBL-*E.coli* Tricycle surveillance, Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP), and antimicrobial consumption.
- 1<sup>st</sup> GLASS report in the fourth quarter of 2017.

#### 1.2 Surveillance of AMR in the food chain

Surveillance of AMR in the food chain is moving from a medical view of bacterial resistance to a more holistic, integrated, multisectoral, “One Health” approach. A revised list of critically important antibiotics and revised WHO AGISAR Guidance on Integrated Surveillance of AMR will be published in early 2017. Between 2010 and 2014, more than 26 AGISAR research projects and country pilot projects were carried out. Current activities include:

- The AGISAR ESBL-*E.coli* “Tricycle” project that aims to develop a global harmonized protocol on integrated surveillance of ESBL-producing *E.coli* in humans, the food chain and the environment
- Participation in Codex Alimentarius Scientific Advice on Antimicrobial Resistance to provide guidance on the design and implementation of a system for integrated surveillance of AMR

- A global sewage surveillance project in 63 countries.

### 1.3 Surveillance of antimicrobial use

Activities include:

- Ongoing integration of the antimicrobial consumption module into the GLASS IT platform
- Ongoing development of protocols for surveys to collect antimicrobial use (prescription and patient purchase) data
- Updating the Essential Medicines List with considerable revision to the chapter on antibiotics. A syndrome-based review of antibiotic treatments for 16 of the most common and/or severe infectious syndromes and five paediatric syndromes is being carried out. For each syndrome, there will be a proposed three-level antibiotic listing. The updated lists will be published in May 2017.
- The priority pathogens list to inform R&D will be available in February 2017.
- Development of policy recommendations on:
  - how AMR information is made available and used in Clinical Practice Guidelines
  - Key messages in antibiotic awareness campaigns
- Support to development of antimicrobial stewardship programmes to ensure appropriate and responsible use of antimicrobials
- The WHO Medicines Price and Availability Monitoring methodology: a mobile app, Survey123 Platform, is in development and there is an antibiotics survey plan for 2017

### 1.4 Surveillance of AMR in gonococci: update from the Gonococcal Antimicrobial Surveillance Programme (GASP)

The magnitude of the gonococcal AMR problem is not completely known due to lack of data in many countries. A recent survey of 108 countries found that less than half (46) countries conducted AMR testing for *Neisseria gonorrhoeae* in the past five years. The lack of information is particularly acute in countries with the highest *N. gonorrhoeae* burden and the greatest need for AMR monitoring. Challenges include: the increasing number of countries participating in GASP; achieving standardized and comparable data; improving on time, ad hoc reporting; information sharing; and sustaining regular monitoring instead of ad hoc surveys.

GASP is in the process of being integrated into GLASS – this will enable both national and regional focal points to access data via GLASS. As it is difficult to culture *N. gonorrhoeae*, molecular approaches are now being considered for monitoring and surveillance. GASP recommends that countries develop their national treatment guidelines based on national surveillance data. With increasing levels of resistance to azithromycin and ciprofloxacin/quinolones, countries must accord funds to surveillance systems – at the moment, budgets are being spent on drugs that are ineffective due to resistance.

### 1.5 Fostering the development of new diagnostic tests

An overview of the process for the development of new diagnostic tests for AMR was presented using the example of a consensus Target Product Profile for a tool to differentiate between bacterial and non-bacterial infections.

## **1.6 Global AMR Surveillance: Update from Food and Agriculture Organization (FAO)**

The FAO AMR multidisciplinary working group and FAO AMR action plan were described. The complex nature of surveillance in this area, which includes meat, aquatic products, agriculture and fisheries was highlighted. Due to poor surveillance and data collection in many countries, estimates of antibiotic consumption in global agriculture vary, ranging from around 63 000 tonnes/year to over 240 000 tonnes/year. Between 70%-80% of antibiotics given to fish are excreted into water and spread through water systems. Between 75%-90% of tested antibiotics are excreted from animals un-metabolized and enter sewage systems and water sources. Information on the health and economic impacts of AMR on livestock and fisheries is lacking in developing countries.

FAO's action plan focuses on four main areas of work

1. Increasing awareness and advocacy on AMR and related threats.
2. Promoting good practices in food and agriculture systems and the cautious use of antimicrobials.
3. Strengthening governance structures, i.e. policies and regulations, related to antimicrobial use in food and agriculture.
4. Developing capacity for surveillance and monitoring of antimicrobial resistance and antimicrobial usage in food and agriculture.

### *Discussion points*

Discussions related to monitoring the quality of antibiotics; surveillance of ESBL –*E.coli* in the non-meat food chain; why there is surveillance of ESBL-*E.coli* and not carbapenemase; who has the lead in setting global standards for surveillance in the food and animal sectors; and how to manage the risk that traditional sources of surveillance information could be diminished/lost through the increased use of rapid point-of-care diagnostics.

## **2. Support to global surveillance**

### **2.1 The Fleming Fund initiative**

This is a £265 million one health programme, funded by UK Government, to support low- and middle-income countries (LMICs) in tackling AMR and to contribute to implementation of the Global Action Plan on AMR. The majority of the investment will be in the form of grants to countries and regions, and through a fellowship scheme, to be implemented by Mott MacDonald. Evaluation of the work will be carried out by ITAD and the University of Sussex, U.K.

An outline of the roadmap to grant making at country and regional level was presented. There will be a strong focus on country ownership. Country assessments to identify candidates for early investment will start in early 2017. These countries will receive support to develop proposals in line with GAP NAPs. There will be two streams: capacity building and surveillance.

*Capacity building* will cover human resources through the Fleming Fund Fellowship scheme. Laboratory infrastructure capacity building will also be supported.

*Surveillance:* the focus will use a one health approach where possible. The protocol developed by LSHTM is designed to assist countries to graduate into the lowest tier of GLASS. While many low-income countries (LICs) are still a long way from this step, the



aim of the Fleming Fund is to get these countries to a stage where they can practically implement GLASS. AMR in animal health, in the environment, antimicrobial use and antimicrobial drug quality will also fall under surveillance.

An 8-month inception period is envisaged, during which time the following activities will be carried out:

- Country assessments: desk based
- Early investment and piloting: four early investment countries
- Allocation models: where is the money best spent?
- Develop call for proposals
- Decide and develop funding streams

Following the assessments, countries will be invited to apply for the first wave of grants in 2017-2018 based on geographical spread and readiness of NAPs. This process will then be repeated in the 2018-2019 and 2019-2020 fiscal years. Fleming Fellowships will be available to all countries that are accessing grants. The Fellowships will provide support through mentorship from competent institutions, secondment, training, support for travel and collaborative projects. Expected outcomes include: better surveillance, improved stewardship, improved treatment, and averting the economic and social burden of AMR.

*Discussion points:*

There was discussion on the need for good coordination between the Fleming Fund and others with similar projects and approaches. The Fleming Fund representative emphasized that they want to complement and synergise investments already made – it is not the intention to complicate the situation, displace funding, or replicate activities. The focus will be on basic microbiology: more complex areas will not be in their purview.

It was noted that there is a concentration of donor support on some geographical areas but not on others. The Fleming Fund acknowledged that this was a challenge as a good coordination forum is lacking. The Fleming Fund representative called on FAO/WHO/OIE or a UN coordinating mechanism for support with this to ensure transparency.

## **2.2 Presentation of the newly established WHO CC Network and work plan**

The newly established WHO AMR Surveillance and Quality Assessment Collaborating Centres Network to support global AMR surveillance capacity building was presented. Network members, drawn from 19 WHO Collaborating Centres, undertake to assist the GLASS Secretariat in the implementation of the 2017-2019 work plan. Four priority areas of work have been identified: capacity building and technical support to microbiology laboratories; capacity building and technical support to surveillance systems; GLASS development; and increasing the understanding of the impact of AMR. Target products for each area of work were defined and Lead CCs assigned. The WHO Collaborating Centre for antimicrobial resistance containment, Sweden (SWE-66) will assist with coordination of the Network for two years on a rotational basis. The report of the meeting, including the terms of reference for the CC Network and the work plan, can be accessed [here](#).

## **3. AMR technical challenges and results from group work outlining next steps to address these challenges**

Presentations were made on key AMR technical challenges following which participants were divided into working groups. Each group was asked to consider questions related to an AMR technical challenge and to produce specific outputs.

### **3.1 Emerging AMR in fungi causing invasive infections in humans**

3.1.1 The top three fungi of concern are: *Candida*, *Aspergillus*, and fungi causing mucormycosis.

*Candida auris*: This yeast usually misidentified as other *Candida* species or *Saccharomyces*, when using biochemical methods (API strips or VITEK-2). *Candida auris* causes outbreaks and is transmitted in healthcare settings. Unlike other *Candida* species, it seems to colonize healthcare environments and skin and poses major infection control challenges. It was noted that with fungi, the higher the minimum inhibitory concentration (MIC) level, the poorer the patient outcome. *Candida auris* is often multi-drug resistant (41%) and associated with higher mortality in Intensive Care Unit in patients with immunosuppression. *C. auris* bloodstream infections are associated with nearly 70% mortality. Whole genome sequencing has produced puzzling findings indicating large genetic differences between continents while highly related within geographic regions. Findings suggest recent independent emergence in at least four places.

*Aspergillus* and the emergence of triazole-resistant *A. fumigatus*. First identified in the Netherlands, 2002-2006, resistance is now found worldwide. Clinical azole resistance rates in the Netherlands are very high at 16%. Azoles are used in crop protection with five azoles being the main drivers for resistance. However, the best antifungal drugs are azoles and as azoles are the only group available, there is a real problem. Invasive aspergillosis is very difficult to diagnose with resistant infections being even more difficult to diagnose. There are limited treatment options and mortality is 50%-100% (median 88%).

*Mucormycosis*: highly resistant organisms that are on the increase.

*The Way Forward* will require good antifungal stewardship and this should be included in programmes. New rapid diagnostic tests can be used to rule out infection and reduce the use of antifungals. There are several new antifungal drugs in development/early trials.

The presentation concluded with an overview of objectives and potential benefits of a global antifungal resistance surveillance system, as well as the potential benefits and risks of including antifungal resistance surveillance in GLASS. These were then discussed in the designated working group.

#### **3.1.2 Feedback from the working group: AMR in invasive fungi**

The group did not consider it appropriate to include AMR in invasive fungi in GLASS at the moment, principally due to the difficulties in some testing systems. However, *Candida* and *Aspergillus* should be considered by GLASS in next the evaluation phase. The group requested the entire meeting (fungal working group, other meeting participants and the GLASS Secretariat) develop antifungal resistance alert criteria and to discuss if *Candida* resistance can be included in the rapid alert component or not.

A situational analysis is required which should include the following: population based resistance rates, burden of disease and laboratory capacity throughout the world. The group agreed to try and put this together.

There is an arrangement for CDC to second a person to WHO as a focal point for fungal infections. Currently, worldwide, there are only three WHO CCs that address antifungal resistance. There is also a need to increase general regional participation to get better laboratory data sets.

A variety of research needs were listed, including PPS and cohort studies, and the group asked if a first burden of disease estimate could be generated by WHO (that includes resistant *Candida*). Given that seven new antifungals are in clinical development, the group wanted to know at what point new treatments become part of the portfolio of work. It was noted that the field is generally under-resourced with public health mycology currently a non-existent discipline that needs support and expertise. The group posed a general question for WHO and others on how to upscale this area.

#### *Discussion points*

With regards to submission of additional pathogens for surveillance reporting, attention was drawn to the “additional status” within GLASS reporting, where any extra information can be added. Therefore, GLASS will eventually allow reporting of antifungal resistance, but criteria need to be developed.

It was noted that a rapid alert applies to any pathogen and not just the eight priority pathogens. The alert system covers both changes in epidemiology as well as new emerging resistance.

In terms of criteria for reporting an unacceptable rate for a life-threatening infection, it was suggested that rates of 3%-5% be used. This may apply in cases of a lethal infection e.g. *Aspergillosis* or candidemia.

### **3.2 Detection of colistin resistance among *Enterobacteriaceae***

3.2.1 Colistin resistance in humans is still uncommon, but is becoming more common among isolates from animals (this may be related to greater use in animals). Susceptibility testing faces a number of complicating factors:

- Colistin diffuses poorly through agar, hence any agar diffusion test (disk or concentration gradient strip) has compromised performance
- The type of microtitre tray used, the type of broth used and the presence of surfactant in the broth can significantly affect the MIC result
- The methanesulfonate form of colistin administered to patients is an inactive prodrug

Few laboratories are able to perform broth microdilution tests and no other drug susceptibility testing requires this method. Therefore, the problem is how to generate and collect reliable data. A number of questions were presented for consideration in the working group.

#### **3.2.2 Feedback from the working group: Detection of colistin resistance**

Guidance for the detection of colistin resistance should not conflict with statements from CLSI/EUCAST. Given the practical issues related to laboratory capacity, colistin resistance testing will be purely for surveillance, not clinical management. The group considered different types of screening approaches. It was emphasized that these should only be used as screening techniques. If resistance is found, it should then be confirmed with a validated MIC assay. The group felt that support should be made available to those countries that wish to acquire the ability to perform assays. The group will prepare more concrete guidance in the coming months.

#### *Discussion points*

Optimism was expressed about the availability of well-performing tests coming to market in the very near future due to recent, new legislation in the U.S.

Some meeting participants wondered about the connection of this topic to GLASS – was the point to implement worldwide testing for colistin resistance? It was clarified that GLASS wants to make countries aware of the limitations of disk diffusion and provide further advice. Most countries use disk diffusion but if they want to be clearer about the result, GLASS will need to guide them. WHO will develop an online document explaining how to detect colistin resistance and how WHO can provide support to countries willing to undertake this testing.

### **3.3 Application of molecular methods (MM) to support AMR surveillance**

3.3.1 The 22-year history of the WHO Global Surveillance of anti-TB Drug Resistance programme was recounted to illustrate the difference that molecular methods can make to surveillance. Molecular methods are particularly pertinent in countries where there is little or no surveillance activity due to weak laboratory capacity. The Democratic Republic of the Congo was cited as an example where, with molecular testing, it has been possible to do a representative national anti-TB drug resistance survey in one year. The advantages of molecular methods are that they: require far fewer cultures e.g. 100 cultures as opposed to 1200-1500 cultures required in a conventional survey; present reduced logistical challenges for sample transport; and reduced demand on laboratories (in terms of both expertise and time). However, it was noted that the test used in this example, Xpert MTB/RIF, alone cannot investigate resistance to anti-TB drugs other than rifampicin and needs to be combined with genome sequencing to explore resistance to additional anti-TB drugs.

Molecular assays have been conducted in 18 countries that have limited culture capacity.

It was noted that the WHO TB Supranational Reference Laboratory Network, with 36 laboratories worldwide, is moving towards surveillance entirely based on molecular technologies, including next-generation sequencing (NGS) which will offer many possibilities in low-resource settings. There is an opportunity for surveillance of AMR in common bacteria to build on existing networks. The presenter urged listeners to give serious consideration to the adoption of molecular testing in LMICs.

#### **3.3.2 Feedback from working group: application of molecular methods**

The objective of this working group was to develop the outline of a road map to provide guidance on molecular testing in GLASS. This will be a document to help the Collaborative Platform decide if MM could be used in GLASS and, if so, how to operationalize the use of these tools in GLASS. The contents will build on work already done by others and will likely be structured into five sections: background; priority pathogens to target; laboratory methods and minimum requirements for laboratory networks; data dissemination; and, operationalization and piloting.

#### *Discussion points*

The great gulf between the reality of poorly resourced LMICs and the world of MM was acknowledged as was the need to explore avenues for GLASS to incorporate MM in the future. All were agreed on the importance of having molecular testing acknowledged within GLASS but as a complement to core GLASS work.

The importance of epidemiological methods as part of comprehensive AMR surveillance was raised. It was suggested that GLASS needs a group to expand epidemiological methods. While not disagreeing with this, it was noted that support to AMR surveillance is still the backbone of GLASS. While too few countries are enrolled in GLASS to support a global point prevalence survey on AMR (as proposed by the Strategic Technical & Advisory Group) it could be possible to put in place surveillance strategies in low-resource settings that can be conducted in a short space of time to inform local efforts to contain AMR. Results from these can in turn inform the global picture. Some CCs have volunteered to assist GLASS to develop protocols for this and enhance epidemiological design for meaningful information.

Other comments noted that it might be easier, better and more cost effective to do genotypic testing for particular types of resistance rather than building laboratory capacity. In terms of data management, it was pointed out that if genetic data is to be part of the data set, GLASS must find a way to take this into account and record the relevant data. It was suggested that a relationship be made between GLASS data and databases that handle whole genome sequences to avoid duplication.

### **3.4 GLASS rapid alert component**

3.4.1 Participants were provided with the first draft of the document, “AMR Rapid Alert Framework and Risk Assessment” that had been prepared by the WHO GLASS Secretariat, and were invited to review, discuss and provide feedback on the document and on the general approach to the question of rapid alert in AMR surveillance.

#### **3.4.2 Feedback from working group: GLASS rapid alert component**

It was agreed that the terms “emergency”, “rapid” and “alert” were misleading in this context. Terminology should be consistent with emerging infectious disease rather than with public health emergencies. It was also agreed that clarification was needed early in the document on the distinction and relationship between IHR reporting and AMR reporting. It was stressed that AMR reporting should reach all constituencies that might discover new resistance, not just public health.

It was noted that not all emerging AMR occurs as an outbreak and not all AMR outbreaks represent new AMR. The Risk Assessment should guide this process.

The provisional watch list will need to be regularly and easily updated (possibly as an annex). Additional resistance to consider including: antifungal resistance; change in epidemiology; change in ecology; increase in occurrence of life-threatening infections.

Reporting of new AMR will be via the GLASS IT platform and should be verified/confirmed by a laboratory with the necessary expertise and capacity. Reporting should be through the Ministry of Health, or if reported directly to WHO from a non-government laboratory, then WHO should inform the Ministry of Health concerned.

It was noted that there is an inherent tension in reporting new AMR and withholding information for later publication purposes. To address this, journals should be encouraged to consider AMR as a public health threat and recognize reporting to GLASS of a new AMR as a citable event.

The group recommended that the risk assessment be condensed and simplified. The risk assessment process should take into account the processes for non-human health sectors,

such as animals and environment, and that a more complete risk assessment may need to be published as a separate document.

The section on risk communication should be expanded and should include clarification of all constituencies that should receive notification of new AMR.

The WHO GLASS secretariat will revise the document ready to be provided to Member States by April 2017. Members of the working group volunteered to help with finalization of the document, although it was noted that no representative from the environment sector was able to participate. IT capacity to report emerging AMR would be in place once Member States had approved the process as outlined in the framework.

#### *Discussion points*

Discussions considered the challenge and necessity of assembling a risk assessment team with representatives from human and animal health and the environment. i.e. multisectoral, at the national level to ensure real progress on the ground. Another challenge will be the need for countries to implement protocols for reporting new types of AMR: Experience from other rapid alert systems indicate that while complete compliance will not happen immediately, over time, buy-in from all sectors should take place. The risk assessment section of the framework document will help in assessing if a newly-identified resistance should be reported or not.

The need for a dissemination strategy to make the rapid alert system more visible among the scientific community, and more broadly, was agreed. An editorial in the Lancet or other prestigious publication was suggested.

#### **4. Concluding remarks**

It was emphasized that GLASS does not intend to duplicate efforts; rather, it will align with existing initiatives and the CC Network will assist with this. The challenge is to make GLASS grow and enhance technical support capacity. The Secretariat is very grateful to the 19 CCs who comprise the Network. CCs have a formal contract with WHO and will lead in the technical areas discussed during this meeting. The CC leads will be contacting partners for contributions in developing target products from the work plan.

While the volume of work is huge, the focus must now be on implementation. Representatives from all six WHO Regional Offices have attended this meeting as they need help with implementation and this must be provided. Special thanks were extended to the Fleming Fund for providing resources to countries for implementation and for participation in GLASS.

On behalf of the GLASS Secretariat, Dr Pessoa-Silva thanked all present for their input as did the Chair Dr Perovic who formally closed the meeting.

## FULL PROCEEDINGS

### **Background:**

The World Health Organisation (WHO) developed the Global Antimicrobial Resistance Surveillance System (GLASS) in accordance with the World Health Assembly (WHA) Resolution WHA68.7 to support the implementation of the global action plan on antimicrobial resistance (AMR).

GLASS collects data on AMR and on the implementation status of national AMR surveillance systems in order to enhance understanding of the extent and impact of AMR on populations and provide evidence for interventions and advocacy.

A call for country enrolment in GLASS was released in March 2016. As at 13 December 2016, 29 countries had enrolled and a further nine had expressed an interest in joining GLASS. Following the first technical meeting of the GLASS Collaborative Platform on early implementation in October 2015, much work has been done to support the process of GLASS early implementation.

In April 2016, a Collaborative Platform working group meeting took place in Geneva, to help develop (i) a proposed guide for implementation of diagnostic stewardship, (ii) a proposed guide for national AMR surveillance system implementation and participation in GLASS, including sample indicators for M&E at national level, and (iii) a core components checklist and questionnaire to assess the national AMR surveillance situation and capacities.

Further support is required to improve GLASS and address the surveillance challenges ahead. The focus of the second meeting of the GLASS Collaborative Platform was on (i) bacterial resistance relevant to human health and (ii) consolidating understanding among and engagement of partners in the work being done.

The purpose of the meeting was to support development, dissemination and implementation of global AMR surveillance.

### **Objectives of the meeting:**

- To update participants on progress achieved over 2016
- To share information on AMR surveillance initiatives
- To outline the next steps to address some specific surveillance challenges:
  - AMR in invasive fungi
  - Detection of emerging colistin resistance in Enterobacteriaceae and application of molecular methods for AMR surveillance
  - Rapid alert component for emerging/new types of AMR within GLASS ]
- To discuss dissemination strategies

### **Expected outputs from the meeting:**

- A common understanding of the status of GLASS development and support to global AMR surveillance efforts
- Defined next steps to address some AMR surveillance challenges
  - AMR in invasive fungi
  - Detection of emerging colistin resistance in Enterobacteriaceae and use of molecular methods for AMR surveillance
  - Rapid alert component for emerging/new types of AMR within GLASS

### **Organization and process of the meeting**

On 15-16 December 2016 WHO hosted a meeting with WHO Collaborating Centres, partner technical institutions and international AMR surveillance networks on the implementation of the WHO global antimicrobial resistance surveillance system (GLASS). The purpose of the meeting is to support development, dissemination and implementation of global AMR surveillance.

The list of participants in the meeting is provided in Annex 1.

The agenda is provided in Annex 2.

The meeting was chaired by Professor Olga Perovic, assisted by Dr Sirenda Vong.

Dr Vong covered some administrative details:

- (i) The meeting will be recorded to help the rapporteur.
- (ii) The record of the meeting will be shared with all participants before being released for public dissemination.
- (iii) He confirmed that all participants completed the WHO standard form for declarations of interest prior to the meeting. Each Declaration received from meeting participants was reviewed in the context of the objectives of the meeting and no conflicts were identified.

### **Welcome and Opening Remarks**

The Chair welcomed everyone and introduced Dr Hajime Inoue, Assistant Director-General WHO Special Representative for Antimicrobial Resistance.

Dr Inoue introduced himself as the successor to Dr Keiji Fukuda who has recently been appointed as Professor of Public Health at Hong Kong University School of Public Health. He wished Dr Fukuda well in his new position. Dr Inoue related how struck he has been since taking up his position by the range of challenges presented by AMR. He recognizes the central role of WHO in combatting AMR and stated that the first priority must be GLASS and ensuring good evidence.

Dr Inoue is involved in preparing for the next G20 meeting in Berlin: WHO proposed that AMR be addressed at the Summit meeting and this has been agreed. Dr Inoue finished by thanking everyone for their commitment and stated that AMR will be his first priority for the next coming years.

At the Chairperson's request, all those present introduced themselves.



## **Day One. Session One: Global surveillance of AMR and antimicrobial use: an update from WHO and partners**

### **1.1 Overview of GLASS and update on early implementation.**

Dr Carmem Pessoa- Silva, Acting Coordinator, GLASS Secretariat

#### **1.1.1 Activities in 2016:**

- Completed activities include: development of the IT platform for aggregated and individual data; adapting WHONET <sup>1</sup> for GLASS; development of an implementation package, with a focus on low-income countries; development of guidelines on integrated surveillance in the food chain (led by WHO/FOS); and the (just established) WHO AMR Surveillance Collaborating Centre Network.
- Links to other AMR data: These include: the Gonococcal Antimicrobial Surveillance Programme (GASP); the ESBL-*E.coli* “Tricycle” programme; the HIV/TB/Malaria cluster within WHO which is working towards creating a common portal; antimicrobial use and consumption data from the Essential Medicines Programme; environmental surveillance data (still in the development stage); as well as collaborating with regional surveillance networks e.g. CAESAR, ReLAVRA and EARS-Net.

Countries enrolled in GLASS since March 2016. 38 have expressed interest and 29 have completed procedures for enrolment. Dr Pessoa-Silva acknowledged and thanked the CAESAR network and colleagues in ECDC, who lead EARS-Net, for their tremendous support motivating countries to join GLASS.

#### **1.1.2 Next steps:**

- Development of a rapid detection and alert framework
- 2<sup>nd</sup> Member States consultation, April 2017 in Sweden. This will be an opportunity to get feedback from Member States on the difficulties they encounter and the feasibility of what GLASS proposes.
- Explore and start planning on: (i) AMR surveillance in invasive fungal infections and (ii) the application of molecular methods for AMR surveillance
- Create new modules in the GLASS IT platform for ESBL-*E.coli* Tricycle surveillance, EGASP, and antimicrobial use and consumption.
- There will be a data call in the second quarter of 2017 with the 1<sup>st</sup> GLASS report due in the fourth quarter of 2017.

GLASS early implementation road map: GLASS is on track

Dr Pessoa-Silva concluded her presentation by thanking the GLASS Secretariat team for all their hard work.

### **1.2 Surveillance of AMR in the food chain**

Dr Jorge Matheu-Alvarez, Project Officer, Food Safety & Zoonotic Diseases Dept, WHO

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<sup>1</sup> WHO microbiology laboratory database software

Dr Matheu opened his presentation by explaining that the approach to surveillance of AMR in the food chain is moving from a medical view of bacterial resistance to a more holistic, integrated, multisectoral, “One Health” approach.

#### *1.5.1 Revised guidance and tools from the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) :*

(i) List of critically important antibiotics (CIA) to support countries in prudent use of antimicrobials. The 5th revision and guidelines will be published in early 2017.

(ii) WHO AGISAR Guidance on Integrated Surveillance of AMR in the food chain: this assists countries and other stakeholders across the one health continuum to establish and develop integrated programmes for surveillance of AMR and antimicrobial use. It includes

- Minimum requirements for integrated AMR surveillance in the food chain
- Guidance on sampling strategies
- Standards for laboratory methods and quality assurance
- Proposes data analyses and reporting methods

Revised guidance will be published in early 2017.

#### *1.5.2 How is the guidance promoted and used?*

- Regional training workshops delivered through the Global Foodborne Disease Network (GFN). This has included laboratory capacity strengthening for integrated surveillance of foodborne diseases and AMR using a “One Health” approach and training of microbiologists and epidemiologists from the human, food and animal sectors. Three workshops were carried out in 2016.
- External Quality Assurance System for food borne pathogens
- Mentoring
- Reference service and laboratory protocols supported by Collaborating Centres (CCs)
- Focused research projects and country pilot projects

Between 2010 and 2014, more than 26 AGISAR projects were carried out.

#### *1.5.3 AGISAR's pilot project approach*

- Supporting pilot research projects at the national level
  - Focused research projects that are smaller scale
  - Country projects on a larger scale
- Call for project proposals every two years, advertised on WHO website for a duration of one month
- Evaluation and selection by a panel of evaluators (AGISAR members)
- A mentor is assigned to each project to support implementation
- Mid-term and final technical and financial reports

#### *1.5.4 Specific objectives of AGISAR projects*

- Increased awareness or/and commitment to prevention and control of foodborne diseases and containment of AMR
- Better prevention and control of foodborne diseases including AMR along the food chain
- More synergies with existing initiatives in the country
- Integrated surveillance implementation, better detection and early warning
- An ability to identify trends in AMR

- Identification of associations between AMR and drug usage in human or animal sectors

#### 1.5.5 *Current activities*

- AGISAR ESBL-*E.coli* "Tricycle" project. AGISAR have decided to focus on the development of a global harmonized protocol on integrated surveillance of ESBL-producing *E.coli* in humans, the food chain and the environment ("Tricycle Surveillance"). This project can be done with minimal resources in-country.
- Codex Alimentarius Scientific Advice on Antimicrobial Resistance. For the 2016 Codex Alimentarius Commission, an Intergovernmental Task Force on Antimicrobial Resistance was established to review the Code of Practice to Minimize and Contain Antimicrobial Resistance, and to provide guidance on the design and implementation of a system for integrated surveillance of AMR.
- Global sewage surveillance project. 80 samples have been collected from 63 countries: initial findings indicate varying levels of resistance in different regions.

### 1.3 **Surveillance of antimicrobial use**

Arno Muller, Dept. of Essential Medicines and Health Products, WHO

Dr Muller provided an overview of AMR-related activities of the Essential Medicines and Health Products Department.

#### 1.3.1 *Monitoring antimicrobial consumption*

Objective: To provide an estimate of the level (quantity) and type of antimicrobials used at country level

Methods: Data collection of national aggregated sales of antimicrobials using the ATC/DDD methodology developed by CCs in 2016

Ongoing integration of the antimicrobial consumption module into the GLASS IT platform so that countries can submit consumption data in the same way that they will submit surveillance data. WHO is supporting 40-50 countries (2016-2017) at country level.

#### 1.3.2 *Antimicrobial use surveys*

Ongoing development of protocols for surveys to collect antimicrobial use (prescription and patient purchase) data:

- In hospitals: Point prevalence surveys (similar to EU, US methodologies) adapted to LMIC contexts
- In community settings: General practitioners, dentists, Community Health Workers, outpatient clinics, hospital emergency departments. Data collection will be at both prescriber and dispenser level.

It is anticipated that the protocols will be published in the 1st quarter of 2017 with piloting of the surveys to be conducted in 2017/2018.

#### 1.3.3 *Essential Medicines List and Priority Pathogens List*

The Essential Medicines List is being updated with considerable revision to the chapter on antibiotics, namely:

- Syndrome-based review of antibiotic treatments for 16 of the most common and/or severe infectious syndromes and five paediatric syndromes

- Review of Systematic Reviews and Clinical Practice Guidelines
- For each syndrome, there will be a proposed antibiotic listing: three levels are proposed (see table below)

<i>Level 1</i> <b>Core/Standard</b>	Antibiotics that are first line choice for empirical therapy (e.g., penicillin G, amoxicillin)
<i>Level 2</i> <b>Targeted/Specific</b>	Antibiotics whose use should be limited to specific subgroups or target populations: patients with penicillin allergy, more severe disease, defined resistance, ...
<i>Level 3</i> <b>Restricted access</b>	<p><b>“Niche”</b> - Antibiotics whose use should be limited to special “niche” indications (e.g. azithromycin in sexually transmitted diseases)</p> <p><b>“Preserved”</b> - Antibiotics that should be preserved and recommended only in limited, specific circumstances (e.g., linezolid for hospital-acquired MRSA pneumonia)</p> <p><b>“Last resort”</b> - Antibiotics whose use should be strictly preserved and “last resort”, (e.g., colistin for multi-drug resistant hospital-acquired infections)</p>

WHO will endeavour to get an agreement with countries on antibiotics of “last resort” and therefore ensure their protection. This will be discussed in March with the Expert Committee.

- For publication in May 2017

#### Priority Pathogens List:

- Identification of priority pathogens for AMR and thus aid the development of research priorities
- Creation of a transparent approach for identifying priority pathogens
- The aim is to adapt the WHO R&D blueprint methodology for prioritizing diseases for use in identifying priority pathogens for AMR
- Work is ongoing and a final draft should be available in February 2017

#### *1.3.4 Policy recommendations*

Clinical Practice Guidelines: The team has surveyed how AMR information is made available and used in Clinical Practice Guidelines (CPGs) as information on resistance is essential to guide choice of antibiotics. A review was conducted of 150 CPGs for five common infectious conditions (respiratory tract infections, urinary tract infections). It was concluded that there is a lack of standards and key information on resistance on which to base antibiotic selection. WHO will provide some solutions and guidance for using AMR information in CPGs.

Key messages in antibiotic awareness campaigns: A comprehensive review of the most recent antibiotic awareness campaigns was conducted. This found messages that are most appropriate for national and local awareness campaign messages. It also identified messages that were not based on evidence and that might be harmful. The strengths and weaknesses of campaigns targeting different stakeholders (prescribers, patients and health systems) were made clear.

#### *1.3.4 Appropriate and responsible use of antimicrobials*

Support to development of antimicrobial stewardship programmes is ongoing. . The 2017 work plan will:

- Review existing antimicrobial stewardship programmes and activities in hospitals and community settings
- Provide guidance for implementation of antimicrobial stewardship programmes in LMICs
- Pilot antimicrobial stewardship programmes in some countries/hospitals/communities

#### *1.3.5 Price and availability of antibiotics*

The WHO Medicines Price and Availability Monitoring methodology will monitor price and medicines availability in pharmacies, hospitals and Central Drug Stores. Initially, a general basket of medicines (including some antibiotics) was considered but it was decided to have specific medicines in class-based baskets with one specifically for antibiotics. A mobile app called Survey123 Platform is in development and there is an antibiotics survey plan for 2017.

### **1.4 Surveillance of AMR in gonococci: update from the Gonococcal Antimicrobial Surveillance Programme (GASP)**

Dr Teodora Wi, Medical Officer, Family, Women and Child Health Dept, WHO

Established in 1993, GASP is a global laboratory network covering over 60 countries in six regions, each with focal points and regional coordinating centres, that monitors the antimicrobial susceptibility of gonorrhoea in participating countries. Dr Wi acknowledged and thanked GASP's regional collaborators and partners. GASP is currently trying to find more partners to provide greater support in the African and Eastern Mediterranean regions.

#### *1.4.1 GASP objectives*

- Ensure adequate sentinel AMR surveillance to inform treatment guidelines in all countries
- Establish a strategy to rapidly detect patients with gonococcal infections, with clinical and/or microbiological treatment failure following treatment with recommended cephalosporin therapy
- Ensure effective clinical management of infected patients and their sexual partners

#### *1.4.2 GASP data 2009-2013*

- 46 countries reported decreased susceptibility to extended spectrum cephalosporins. This means that guidelines will need to be changed again in the near future
- 10 countries reporting treatment failure to extended spectrum cephalosporins
- 17 countries reported resistance to azithromycin in > 5% of gonorrhoea isolates
- Majority of countries reported high level of resistance to quinolones

WHO is working to make GASP as effective as possible and address its many challenges, including limited national leadership, commitment and funding in many countries. The magnitude of the gonococcal AMR problem is not completely known due to lack of data in many countries. A recent survey of 108 countries found that less than half (46) conducted AMR testing for gonorrhoea in the past five years. The lack of information is particularly acute in countries with the highest gonorrhoea burden and the greatest need for AMR

monitoring. These are often countries with suboptimal diagnosis and surveillance capacity, freely available antibiotics (including counterfeit drugs), and lack of drug quality control contributing to the rapid development of resistance. They are also the countries most likely to rely on syndromic management of sexually transmitted infections (STIs), leading to a shortage of samples for AMR monitoring and lack of capacity and supplies for specimen collection, culture and sensitivity testing. Cultures are also carried out less frequently in more developed countries as diagnosis is improved by the use of molecular methods. Countries in Africa, South-east Asia and the Eastern Mediterranean region (as well as Eastern Europe and Central Asia) particularly, do not have functioning programmes in place to assess gonococcal antimicrobial susceptibility.

#### 1.4.3 Challenges

- Number of countries participating in GASP – more are needed
- Standardized and comparable data (Threshold > 5% resistance)
  - Sample size is small
  - Variable antibacterial susceptibility testing (AST) methodologies
  - Quality data (laboratory capacity)
- Delayed, ad hoc reporting, therefore an early warning system does not exist. There is a need for:
  - Timely release of data
  - Collection of enhanced epidemiological and clinical information linked to microbiological information
  - Monitoring of antimicrobial treatment
- Sharing of information
- Sustaining regular monitoring instead of ad hoc surveys

The need now is to integrate GASP into GLASS and thus enable regional focal points to access data via GLASS – the integration process is in progress.

Molecular approaches: As it is difficult to culture gonorrhoea, molecular approaches are now being considered to monitor AMR and enhance surveillance. A number of countries have started work on this.

#### 1.4.4 GASP recommendations

- Countries should develop their national treatment guidelines based on national surveillance data.
- With increasing levels of resistance to azithromycin and ciprofloxacin/quinolones, countries must accord funds to surveillance systems – at the moment, budgets are being spent on drugs that are ineffective due to resistance.

### 1.5 Fostering the development of new diagnostic tests

Dr Francis Moussy, Essential Medicines and Health Products Dept., WHO

Dr Moussy opened his presentation with a disclaimer that not as much progress as WHO would have liked to have made has been made due to lack of resources.

#### 1.5.1 What is needed to facilitate the development of diagnostic tests for AMR?

- Coordinate the mapping of existing diagnostic tools for AMR

- Assess the needs and develop consensus Target Product Profiles (TPPs), with very clear definitions of point of care
- With various organizations e.g. Foundation for Innovative New Diagnostics (FIND), initiate (a) partnership(s) to develop priority AMR diagnostic tests based on the TPPs
- De-risk the development of new AMR diagnostics for companies (e.g. coordinate market analysis for diagnostics in response to the TPPs, advance market commitments, prizes, grant, etc).

The issues of access and use of the newly developed tests will also need to be addressed.

#### *1.5.2 Why develop Target Product Profiles for diagnostics?*

- To clearly inform the diagnostic industry and other R&D groups about the types of diagnostics that are needed (e.g. TB, Ebola, Zika, viral vs bacterial differentiation).
- To specify the desired (or acceptable) characteristics of the needed diagnostics.
- Funders, procurers and regulatory agencies also use such TPPs to focus their activities.

#### *1.5.3 What is included in a diagnostic TPP?*

- Scope: intended use, setting, user, target population
- Performance and operational characteristics
- Price
- Usually includes two categories: "acceptable" versus "desired"

#### *1.5.4 Example of a consensus TPP in an expert driven approach. Steps taken to develop a tool to differentiate between bacterial and non-bacterial infections*

1. Identification of the need during a biomarker workshop (September 2015)
2. Draft TPPs based on available literature
3. Circulated to 16 experts from academia, nongovernment organizations (NGOs) and WHO
4. Refined draft circulated prior to a face-to-face meeting
5. Consensus meeting with all experts
  - Ranking of priorities for in-depth discussion based on agreement/dissension in commenting round
  - All discussions noted and consensus achieved by majority vote
6. Publication of final TPPs in public domain

Dr Moussy described some selected characteristics of the TPP i.e. scope and test performance (acceptable and desired data). Following this, the TPP was published on the WHO and FIND websites as well as in peer reviewed journals, disseminated at conferences and actively to industry partners. In the future, AMR will be included in the new list of essential diagnostics, which may be an incentive for companies to become involved.

Dr Moussy provided a list of TPP working group partners and funders and gave special thanks to Sabine Dittrich (FIND) for providing several slides for the presentation.

## 1.6 Global AMR Surveillance: Update from the Food and Agriculture Organization of the United Nations.

Julio Pinto, FAO AMR Working Group

### 1.6.1 Overview

The presenter acknowledged that the animal and food sectors were behind the health sector in terms of the design of surveillance strategies and platforms to collect surveillance data. Mr Pinto presented the FAO AMR action plan that is based on three pillars: practice, governance and evidence and described the AMR multidisciplinary working group. He also highlighted the recent publication “Drivers, dynamics and epidemiology of antimicrobial resistance in animal production”.

It was noted that antibiotics are used three times more frequently in animals than in humans. Mr Pinto provided an overview of the global demand for meat and eggs (2005 v 2050) highlighting the ever-increasing demand. In the animal sector, the use of antimicrobials in animal husbandry can be seen to have an economic justification in the need to feed an increasing human population. The presenter indicated that the use of antimicrobials for increased productivity will probably continue in many regions. LMICs are recording increased meat demands. It will be important to send the right message about the need for responsible use of antimicrobials but it is likely that they will continue to be used for productivity in the food animal sector.

Surveillance in this area is complex – including meat, aquatic products, agriculture and fisheries - and it needs to be more integrated. There is a need to define what “one health” means and where surveillance is needed.

Mr Pinto presented an AMR risk map drawn from the results of a recent study by Van Boeckel et al. (2015) that used statistical models based on data from a limited number (32) of countries to estimate the extent of antimicrobial usage in food-producing animals at global level. Due to poor surveillance and data collection in many countries, estimates of antibiotic consumption in global agriculture vary, ranging from around 63 000 tonnes/year to over 240 000 tonnes/year. Between 70%-80% of antibiotics given to fish are excreted into water and spread through water systems. Antibiotics used for crops are relatively low in comparison to the quantities used in livestock, with estimates ranging from 0.2%-0.4% of total agricultural antibiotic consumption. Between 75%-90% of tested antibiotics are excreted from animals un-metabolized and enter sewage systems and water sources. Information on the health and economic impacts of AMR on livestock and fisheries is lacking in developing countries.

### 1.6.2 Issues:

- Complex due to different sectors, vested interests, a complex interface, farmer incentives etc.
- The message exists on how the problem can be reduced: what are needed are political will and technical capacities
- Need for evidence. Surveillance of antimicrobial use and resistance can help to provide the evidence base for plans and policy formulation
- How do we implement One Health surveillance effectively for AMR in this complex livestock/human/ecosystem interface? Surveillance needs to be prioritized and cost-effective - it is not feasible to conduct surveillance in all sectors and it will be context dependent. Risk assessment must be used in the prioritization process.

### 1.6.3 Objectives of a surveillance programme for AMR



- to monitor food animal and human consumption of antimicrobial agents
- to monitor occurrence of AMR in bacteria isolated from food animals, food and humans (e.g. salmonella, campylobacter)
- to study and provide evidence on the association between antimicrobial consumption and antimicrobial resistance
- to support decision making by identifying routes of transmission (critical control points) and high risk interfaces or production systems for further research.

#### 1.6.4 *AMR surveillance plan*

- Engagement of livestock farmers, value chain actors, communities.
- Need good information. How much is used and what is being prescribed/used
- How to collect information. If global standards are available from WHO, these can be used by FAO.
- Risk analysis/risk communication for supporting risk-based surveillance.
- AI and Recording systems: origin/destination, movement, treatment, history of a group or individual
- Setting up priorities and defining targets and evaluation

#### 1.6.5 *Key messages*

- AMR is a bidirectional zoonosis. It also has multidirectional links to other environmental compartments, including aquaculture, food plants and water.
- Major gaps exist in surveillance of antimicrobial use and resistance and there needs to be more open data sharing in all sectors
- Integrated surveillance systems would enable data comparison from food-producing animals, food products and humans
- Surveillance is hampered by a lack of implemented global standards
- Multisectoral/One Health approach is required
- The food and agriculture sector including the livestock sector is part of the problem but also part of the solution

#### 1.6.6 *FAO's Action Plan* focuses on four main areas of work to tackle AMR.

1. Increasing awareness and advocacy on AMR and related threats.
2. Promoting good practices in food and agriculture systems and the cautious use of antimicrobials.
3. Strengthening governance structures, i.e. policies and regulations, related to antimicrobial use in food and agriculture.
4. Developing capacity for surveillance and monitoring of antimicrobial resistance and antimicrobial usage in food and agriculture.

### 1.7. **Discussion points following the presentations**

1.7.1 Surveillance of antimicrobial use: are you looking at the quality of antibiotics? It is difficult to measure in a questionnaire but it is important. Yes, WHO has a team that monitors substandard, falsified and counterfeit medical products which includes antibiotics.

1.7.2 Clinical Guidelines – is this a framework or a local activity? This will be a national-level activity.

1.7.3 There was a comment on the fact that there can be many different antibiotic surveillance systems within one country. GLASS is ideal as one system and will help to avoid this in the future. Countries should be advised to have one system only and learn from the mistakes of others.

1.7.4 Surveillance of AMR in the food chain: the impressive progress made by WHO in this area and others was acknowledged. Will there be surveillance of ESBL *-E.coli* in the non-meat food chain? For now the focus will be on food animals and will not include vegetables or fruit.

1.7.5 Rapid diagnostic tests: as we increase the use of rapid point-of-care (POC) diagnostics, there is a risk that traditional sources of surveillance information will be lost. Does GLASS have a plan to capture information from the use and results of POC tests? There is a need to keep both nucleic acid-based and culture tests.

How do we capture data if conducted outside of a surveillance system? When we promote the use of decentralized tests, we must make sure that those tests have the ability to send data out, and this must then be collected and analysed. Acknowledged that simple tests such as malaria RDTs will be difficult to capture but more sophisticated ones e.g. GeneXpert have the ability to send data.

1.7.6 How do we make data timely enough to become cutting edge? Acknowledgement that timeliness is an issue: a new system is needed hence it is sensible to integrate into GLASS.

1.7.7 There was a discussion about the merits of more basic versus more sophisticated tests – the conclusion being that one method doesn't fit all organisms.

1.7.8 There was discussion that while the ESBL work is good, there should also be surveillance of carbapenemase. As the focus of GLASS is on LMICs and the need to carry out surveillance in all sectors, ESBL was chosen as it fits the criteria and can be followed to assess effectiveness of interventions. Carbapenemase is not easy to detect and is mostly found in the food chain and not in humans.

1.7.9 It was clarified that there is a technical support mechanism within FAO, similar to a WHO CC (but not specifically for AMR), that provides support for laboratory diagnostics, surveillance, risk analysis, epidemiological training in country. FAO also plans to establish centres in South-East Asia and Africa.

1.7.10 The question was posed regarding who has the lead in setting global standards for surveillance in the food and animal sectors? Many are working in this area but the lead is unclear. In response, the FAO representative noted the complex and multisectoral nature of surveillance in this area. OIE has plans for a global database on antimicrobial use and it is hoped they will develop global standards. A global set of minimum standards that can be shared with different platforms must be defined.

## **Day One. Session Two: Support to global surveillance**

## 2.1 Fleming Fund initiative

Dr Charles Penn and Dr Toby Leslie

### 2.1.1 *What is the Fleming Fund?*

A £265 million “one health” programme to support LMICs in tackling AMR and to contribute to implementation of the Global Action Plan on Antimicrobial Resistance. It is part of the UK Government’s Official Development Assistance strategy to promote the economic development and welfare of developing countries. The aim is to ensure that Fleming Funds add value given other global actors in the field of AMR and not duplicate efforts. The geographical focus for Fleming Funds is sub-Saharan Africa, south Asia and South-East Asia.

### 2.1.2 *Aim of the Fund*

To strengthen surveillance for AMR and collection of data on antimicrobial use in LMICs through grants to countries for:

- Implementation of standard, quality driven protocols for sample and data collection, analysis and reporting that take into account the need for clinical information and epidemiology. This includes data on the sale and use of antimicrobial medicines, particularly antibiotics.
- Laboratory capacity for bacterial diagnosis and AST
- Enabling the sharing of drug resistance data locally, regionally and internationally (e.g. WHO GLASS, Burden of Disease)
- Advocating the application of these data to promote the rational use of antimicrobials for human health, animal health and agriculture

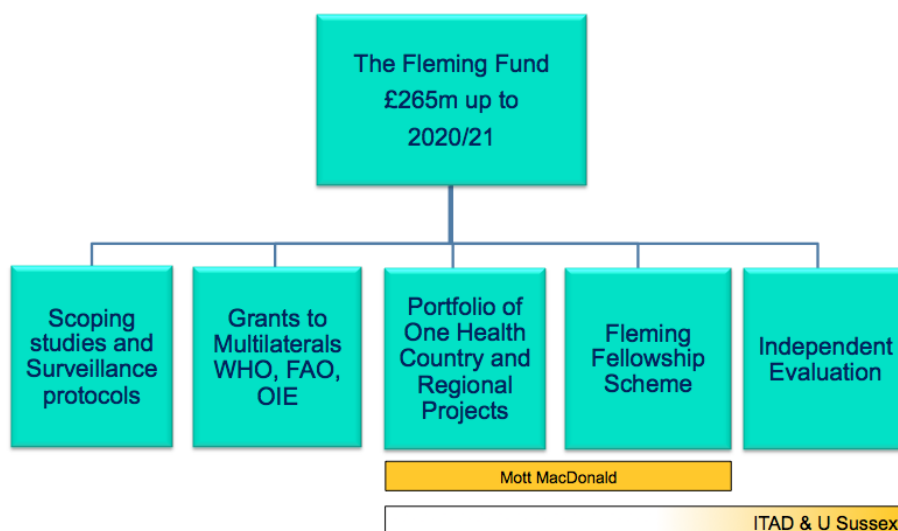
### 2.1.3 *Core Principles*

- A one health approach to human and animal health and AMR in agriculture and the environment.
- In-country ownership through national action plans
- Sustainability.
- Alignment of activities and systems – from national to regional to international.

At the heart of the programme will be commitments to evaluation, continued improvement and value for money.

### 2.1.4 *Programme structure*

## Programme Structure



Scoping studies have been undertaken to document what has been done and these studies will be made publically available.

- An Analysis Of Approaches To Laboratory Capacity Strengthening For Drug Resistant Infections In Low And Middle Income Countries. Imelda Bates et al LSTM, Anthony Scott et al LSHTM
- An Analysis Of Networks And Education Resources Supporting Drug Resistant Infection Surveillance In Low And Middle Income Countries. Elizabeth Ashley et al MORU; Imelda Bates et al LSTM
- An Analysis of The Animal/Human Interface With A Focus On Low And Middle Income Counties. Stephen Baker et al OUCRU Viet Nam; Jonathan Rushton et al RVC London

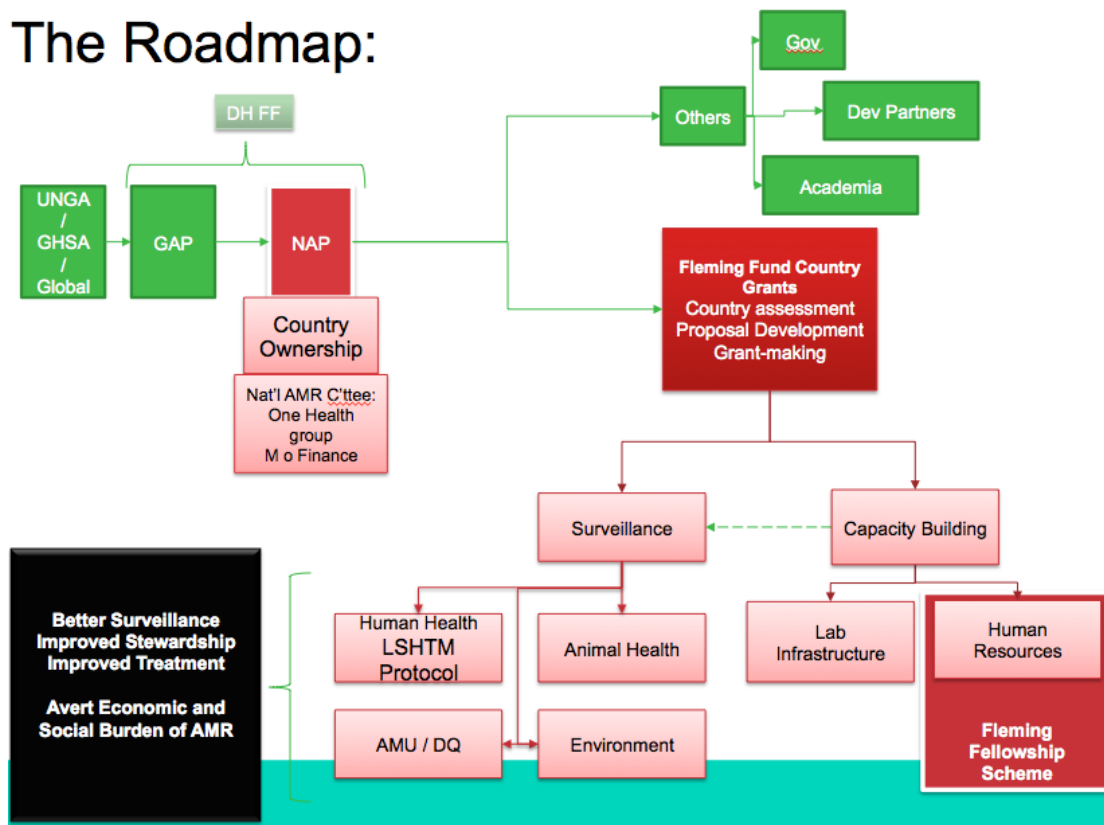
A surveillance protocol has been developed with LSHTM to help countries participate in GLASS.

The majority of the investment will be in the form of grants to countries and regions, and a fellowship scheme, to be implemented by Mott MacDonald. Evaluation of the work will be carried out by Itad and the University of Sussex, UK.

### 2.1.5 The Roadmap

An outline of the Roadmap to grant making at country and regional level was presented with a strong focus on country ownership. Country assessments to identify countries for early investment will start in early 2017. These countries will receive support to develop proposals in line with GAP NAPs. There will be two streams: surveillance and capacity building.

# The Roadmap:



Capacity building will cover human resources through the Fleming Fund Fellowship scheme – a process of medium-to-long term mentorship. More information on this will be released over the next 3-4 months. Laboratory infrastructure capacity building will also be supported.

Surveillance: the focus will use a one health approach where possible. The protocol developed by LSHTM is designed to assist countries to graduate into the lowest tier of GLASS. While many LICs are still a long way from this step, the aim of the Fleming Funds is to get these countries to a stage where they can practically implement GLASS. Animal health, the environment and antimicrobial use and drug quality will also fall under surveillance.

The outcomes will be: better surveillance, improved stewardship, improved treatment, and averting the economic and social burden of AMR.

Getting political will across the different sectors via the Prime Minister or President will be essential. There is a lot to do over 4.5 years in approximately 30 countries. Activity will concentrate on doing relatively small building-block work initially and trying to do it well. The process will begin in-country with the AMR coordination committee. Significant technical assistance will be required to achieve practicable, executable plans and generous technical assistance support monies exist for countries to develop their NAPs.

## 2.1.7 Preparatory Work

8-month inception period:

- Country assessments: desk based
- Early investment and piloting: four early investment countries
- Allocation models: where is the money best spent?
- Develop call for proposals
- Decide and develop funding streams

Funding applications. The Fleming Fund will implement a phased approach. Following the assessments, countries will be invited to apply for the first wave of grants in 2017-2018 based on geographical spread and readiness of NAPs. This process will then be repeated in the 2018-2019 and 2019-2020 fiscal years. The number of countries in Wave 1 has not been decided yet. It is anticipated that between 9 and 16 countries will be in the first round.

Fleming Fellowships: These will be available to all countries who are accessing grants. The Fellowships will provide support through mentorship from competent institutions, secondment, training, support for travel and collaborative projects.

#### 2.1.8 Discussion points:

1. Coordination: The presenters were asked about coordination between the Fleming Fund and others with similar projects and approaches. The Fleming Fund wants to complement and synergise investments already made. It is true that it is a very busy space at the moment but laboratory capacity support encompasses many different disciplines and diseases. The Fleming Fund is working strongly and building relationships with UN and US agencies and using UK Government diplomatic networks also. It does not want to complicate the situation, displace funding, or replicate activities. The focus will be on basic bacteriology and microbiology: more complex areas will not be in their purview.

It was noted that WHO has a group working on corporate fund raising and coordination of donors. This group indicates gaps to donors but cannot oblige donors to fill those gaps. In addition to coordination, implementation can also be a challenge especially in limited resource settings or where there are many partners with little coordination in-country.

2. Geographical area support: It was noted that there is a concentration of donor support on some geographical areas but not on others. The Fleming Fund acknowledged that this was a challenge as a good coordination forum is lacking. The Fleming Fund representative called on FAO/WHO/OIE or a UN coordinating mechanism for support with this to ensure transparency. He assured listeners that the Fleming Fund is will coordinate well with others in the countries where they will be working.
3. Surveillance of healthcare acquired infections included? Yes.

## 2.2 Presentation of the newly established WHO CC network and work plan

Dr Malin Grape provided an update on the establishment of the WHO AMR Surveillance and Quality Assessment Collaborating Centres Network to support global AMR surveillance capacity building. It was established in response to a Member States' request in Resolution WHA68.7. Network members, drawn from 19 WHO Collaborating Centres, undertook to assist the GLASS Secretariat in the implementation of the 2017-2019 work plan. Four priority areas of work were identified: capacity building and technical support

to microbiology laboratories; capacity building and technical support to surveillance systems; GLASS development; and increase understanding of impact of AMR. Target products for each area of work were defined and Lead CCs assigned. The WHO Collaborating Centre for antimicrobial resistance containment, Sweden (SWE-66), will assist with coordination of the Network for two years on a rotational basis. Dr Grape noted that the role of CCs is mandated by WHO and the Network can act as a platform to collaborate with other partners, many of whom are present at this meeting. More details can be found in the meeting report available [here](#).

The Chair thanked all and closed the session.

## **Day One. Session Three: AMR technical challenges**

Chair: Dr Sirenda Vong

### **3.1 Emerging AMR in fungi causing invasive infections in humans**

Dr Tom Chiller, Chief, Mycotic Diseases Branch, CDC, USA.

#### *3.1.1 Overview*

The top three fungi of concern are *Candida*, *Aspergillus*, and fungi causing Mucormycosis

##### *Candidia*

- Risk factors: ANTIBIOTICS, immunosuppression, neutropenia, Intensive Care Unit care, abdominal surgery
- Humans are colonized
- Infected by our own strains or by acquisition in a healthcare setting
- Bloodstream infections (BSI) and invasive abdominal candidiasis
- #1 cause of healthcare-associated BSI in the U.S; 6% of all HAIs

##### *Molds*

- Risk factors: neutropenia, immunosuppression, diabetes
- The whole world is colonized
- Infected by inhaling airborne spores
- Lungs and sinuses, and can disseminate
- Aspergillosis is #1 ; Mucormycosis is #2

Different species carry different resistances: therefore as more species come into play, more treatments are used and resistance increases. Drug resistance is becoming more evident – 12% and 10% levels have been recorded at U.S. surveillance sites. It should be noted also that with fungi, the higher the minimum inhibitory concentration (MIC) level, the poorer the patient outcome. In multiple centres, resistance has been associated with death after adjustment for Intensive Care Unit (ICU) status and degree of immunosuppression.

#### *3.1.2 Candida auris: A global emerging multidrug-resistant yeast*

Dr Chiller gave an overview of the global emergence of this resistance 2009 – 2015. Starting as an ear infection in Japan, the first report of a *C. auris* BSI was recorded in 2011.

The US Centers for Disease Control and Prevention (CDC) launched its international *C. auris* work in Pakistan 2014-2015. *C. auris* is concerning as

- It is multi-drug resistant, exhibiting resistance to fluconazole, variable susceptibility to other azoles, amphotericin B, and echinocandins; and
- It is challenging to identify and is often mis-identified as *C. haemulonii*.

#### *C. auris* early epidemiology

- Patients of all age ranges (Neonatal ICU infants → elderly)
- Similar risk factors as for other *Candida* species
  - Diabetes
  - Antibiotic use
  - Recent surgery
  - Presence of a central venous catheter
- May occur in conjunction with other *Candida* species
- Patients on antifungal treatment when *C. auris* isolated
- Median time from admission to infections: 17 days
- Mortality ~70%;
  - 100% in Venezuela in NICU infants

#### Antifungal susceptibility

- 93% resistant to fluconazole
- 54% resistant to voriconazole
- 35% resistant to amphotericin B
- 7% resistant to echinocandins
- 41% multi-drug resistant isolates
- 4% resistant to all three major antifungal classes

#### Why is there concern about *C. auris*?

- Is multi-drug resistant
  - Some isolates resistant to all three major antifungal classes
- Can be misidentified
  - Usually misidentified as other *Candida* species or *Saccharomyces*
  - MALDI-TOF2 can detect *C. auris*
- Causes outbreaks and is transmitted in healthcare settings
  - Unlike other *Candida* species, it seems to colonize healthcare environments and skin
  - Major infection control challenges
- Puzzling findings from Whole Genome Sequencing (WGS):
  - Large genetic differences between continents
  - Highly related within geographic regions
  - Suggests recent independent emergence in at least four places

#### 3.1.3 *Aspergillus: Emergence of Triazole-Resistant A. fumigatus*

Triazole-Resistant *A. fumigatus* was first identified in nine patients in Netherlands, 2002-2006 and is now found worldwide. Clinical azole resistance rates are currently very high in the Netherlands at 16%. Resistance has also been found in people's homes. In the Netherlands, resistance is thought to be driven by the tulip bulb industry while in Britain, resistance spreads via the onion crop but is also found in other settings. Azoles are used

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<sup>2</sup> MALDI-TOF (Matrix Assisted Laser Desorption/Ionization Time of Flight) is an automated mass spectrometry and software system designed for rapid microbial identification



in crop protection with five azoles being the main drivers for resistance. However, the best drugs are azoles and as azoles are the only group available, there is a real problem.

#### Challenges Posed by Triazole-Resistant *A. fumigatus*

- Invasive aspergillosis is very hard to diagnose
- Resistant infections are even harder to diagnose
  - Susceptibility testing is not routinely performed
  - Resistance is missed due to co-infection with susceptible strains
  - New polymerase chain reaction (PCR) assay, but concerns of limited sensitivity
- Limited treatment options
- Mortality 50-100% (median 88%)
- Fungicides are needed to feed the world

3.1.4 *Mucormycosis*: highly resistant organisms on the increase

3.1.5 *The Way Forward*

#### Stewardship

- Anti-bacterial use is the greatest factor associated with Candidemia
- Antifungal stewardship needs to be included in programs
- New rapid diagnostic tests can be used to rule out infection
- Less use of antifungals

#### Pipeline of new, better drugs

- Several new antifungal drugs in development/early trials
- New mechanisms of action
- New delivery

#### AMR in fungi and GLASS

1. *Candida*
  - a. Easy to culture - start with blood (although other sites)
  - b. Species level data an important association with resistance
    - i. *C. glabrata*, *C. parapsilosis*, *C. auris*
  - c. Antifungal susceptibility testing (AFST) more difficult but it is done globally
  - d. Sentinel systems are present globally
  - e. Most concerning for resistance and burden
2. *Aspergillus*: Just *fumigatus* – azole
3. *Mucormycosis*: Challenging but on the increase

Dr Chiller concluded his presentation with an overview of objectives and potential benefits of a global antifungal resistance surveillance system, as well as the potential benefits and risks of including antifungal resistance surveillance in GLASS.

### 3.2 Detection of colistin resistance among *Enterobacteriaceae*

Christopher Oxenford, Health Emergencies Programme, WHO

#### 3.1.1 Overview

Colistin is a polymyxin, discovered in the 1950s. Initially, there was little systemic use of colistin owing to neural and renal toxicity but interest has grown in it as an agent of last resort in recent years.

Colistin resistance: Resistance among isolates from humans is still uncommon, but is becoming more common among isolates from animals (related to greater use?)

#### 3.1.2 Susceptibility testing - Complicating factors

- Colistin diffuses poorly through agar, hence any agar diffusion test (disk or concentration gradient strip) has compromised performance
- The type of microtitre tray used, the type of broth used and the presence of surfactant in the broth can significantly affect the MIC result
- The methanesulfonate form of colistin administered to patients is an inactive prodrug

#### 3.1.3 Current recommendations

Colistin (polymyxin E) MIC determination is associated with several methodological issues. These have been investigated by the CLSI-EUCAST joint Polymyxin Breakpoints Working Group and the following method for determination of colistin MIC was agreed:

- Reference testing of *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. is by the ISO-standard broth microdilution method (20776- 1).  
Note:
  - Cation-adjusted Mueller-Hinton Broth is used
  - No additives may be included in any part of the testing process (in particular, no polysorbate-80 or other surfactants)
  - Trays must be made of plain polystyrene and not treated in any way before use
  - Sulphate salts of polymyxins must be used (the methanesulfonate derivative of colistin must not be used - it is an inactive pro-drug that breaks down slowly in solution)
- Susceptibility testing by other methods, including agar dilution, disk diffusion and gradient diffusion, cannot be recommended until historical data have been reviewed or new study data have been generated. Work on these methods is ongoing.

#### 3.1.4 Challenges

- Few laboratories are able to perform broth microdilution tests
  - Lack the training and supplies
- No other drug susceptibility testing requires this method
- How to generate and collect reliable data?

#### 3.1.5 Questions to consider

1. What is a sustainable model for colistin resistance surveillance.
  - Ensuring a NRL has the capability to perform these tests
  - Establishment of a referral mechanism in-country

- Recommendations on which strains should be tested, (only multi-resistant strains, carbapenemase and/or ESBL producers?) or only strains from invasive disease or as many strains as possible
2. What technical support can be provided to countries that wish to monitor colistin resistance
    - Training to perform and interpret the tests
    - Provision of reagents and control
    - International referral of isolates
    -
  3. What about monitoring for resistance genes?

### 3.3 Application of molecular methods to support AMR surveillance

Matteo Zignol, Scientist & Chris Gilpin, Scientist, Laboratories, Diagnostics and Drug-Resistance Unit, WHO

#### 3.3.1 *Global surveillance of anti-TB drug resistance and experiences with molecular methods (MM)*

The 22-year history of this WHO programme was recounted to illustrate the difference that molecular methods can make to surveillance. The laboratory component is the backbone of drug resistant-TB surveillance and the WHO TB Supranational Reference Laboratory Network now has 36 laboratories worldwide. It is moving towards surveillance entirely based on molecular technologies, including next generation genome sequencing (NGS) which will offer many possibilities in low-resource settings. There is an opportunity for AMR surveillance to build on existing networks. It was noted that the adoption of molecular testing should be viewed in the same way that mobile phones were adopted in LMICs.

There are still countries where there is little or no surveillance activity due to weak laboratory capacity e.g. the Democratic Republic of the Congo (DRC). However, with molecular testing, it has been possible to do a representative national anti-TB drug resistance survey in one year. The advantage of molecular methods is that they require 100 cultures as opposed to 1200-1500 cultures required in a conventional survey. The survey design is given below.

TB laboratory capacity in DRC:

- Good capacity of sputum-smear microscopy
- Limited capacity for culture
- No capacity for drug susceptibility testing
- Availability of Xpert MTB/RIF3 in multiple sites

#### 3.3.2 *Xpert MTB/RIF for surveillance*

- Reduces logistic challenges for sample transport
- Reduces demand on laboratories (expertise and time)

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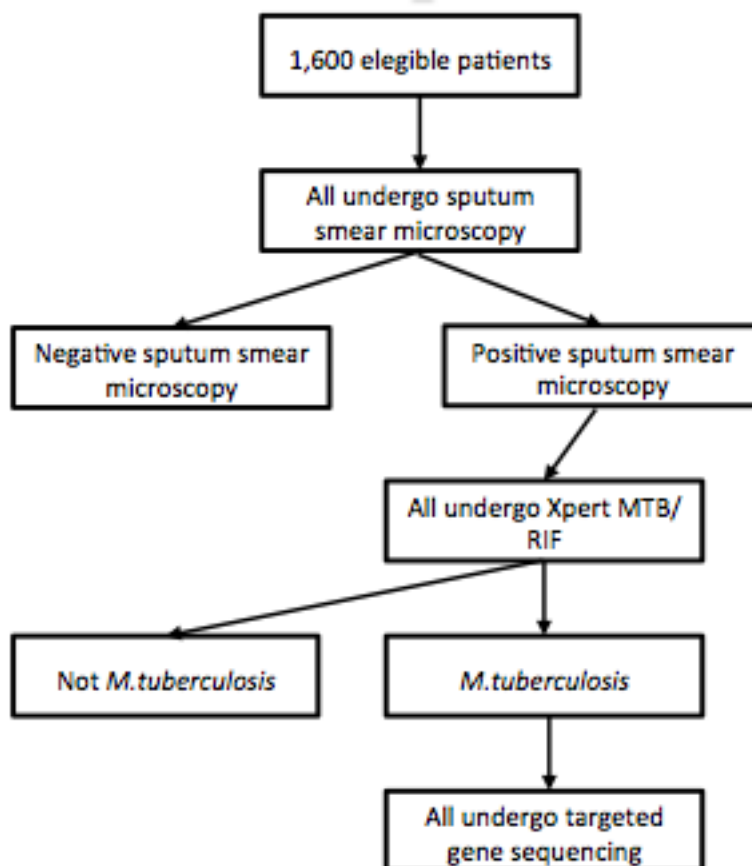
<sup>3</sup> The Xpert MTB/RIF assay is a test that contributes to the rapid diagnosis of TB disease and rifampicin resistance

- Xpert MTB/RIF alone cannot investigate resistance to anti-TB drugs other than rifampicin
- Needs to be combined with genome sequencing to explore resistance to additional anti-TB drugs

### 3.3.3 Characteristics of sequencing

- Sequencing is the most accurate molecular test available
- High throughput: up to ~ 200 strains per run/3-4 days
- Cheaper than standard phenotypic testing (as low as 50 USD per strain and it is going down)
- Test accuracy:
  - RIF: possibly equivalent to phenotypic test
  - PZA: possibly equivalent to phenotypic test
  - INH: low sensitivity compared to phenotypic test
  - FQL: low sensitivity compared to phenotypic test
  - AGL: low sensitivity compared to phenotypic test
  - New drugs (BQL, DLM): to be studied

### 3.3.4 DRC Survey design



Molecular assays used in 18 surveys:

Surveys can now be conducted in countries with limited culture capacity

- Xpert MTB/RIF: already used in: Burkina Faso, Cote d'Ivoire, DR Congo, Djibouti, Lao PDR, Pakistan, Papua New Guinea, Senegal, Zimbabwe

- planned to be used in 2016 in: Eritrea, Ethiopia, Indonesia, Malawi, Swaziland
- Line Probe Assays: already used in: Lesotho, Nigeria, Rwanda, Sudan, Tanzania.

A point of information was given: a company in Oxford, U.K. is producing a matchbox-sized sequencer that can be plugged into the computer/mobile phone and will be on the market soon. Molecular technology needs to be discussed now and we need to move with it.

### 3.4 GLASS rapid alert component: draft protocol

The draft protocol for a rapid alert component within GLASS was distributed for discussion in the group work session.

### 3.5 Group work: Outlining the next steps to address surveillance challenges

Participants were divided into working groups (see table) and a list of question guides and expected outputs were allocated. Following discussions, the meeting adjourned for the evening. Feedback was given on the morning of day two.

Group work: Outlining the next steps to address the surveillance challenges		
<b>Group I:</b> Rapid Alert	<b>Group II</b> AMR in invasive fungi	<b>Group III</b> Detection of colistin resistance & Application of molecular methods

Question guides and expected outputs for working groups

#### 3.5.1 Group I. Emerging AMR: rapid alert and risk assessment framework

Participants were provided with the first draft of document, “AMR Rapid Alert Framework and Risk Assessment” that had been prepared by the WHO GLASS Secretariat, and were invited to review, discuss and provide feedback on the document and on the general approach to the question of rapid alert in AMR surveillance. Activities of the working group for this 2nd meeting were to:

- Discuss and advance the draft
- Define next steps for finalizing the document by Feb 2017
- Present document to Member States consultation in April 2017

#### 3.5.2 Group II.

##### AMR in fungi: questions

I. Objectives and potential benefits of global antifungal resistance (AFR) surveillance

1. Which would be the specific objectives of AFR surveillance – local and global level?
  - Estimate the burden of resistant invasive fungal diseases
  - Monitor trends in antifungal resistance
  - Inform clinical guidelines for antifungal treatment

- Improve good clinical practices: for diagnosis, treatment and clinical care and infection prevention and control
- II. Potential benefits of implementing AFR surveillance
  - Improve understanding of impact of AFR
  - Strengthen the performance of the clinical laboratories for detection, identification and antifungal susceptibility testing (AFST)
  - Promote standardization/definition of diagnostic tools, AFST and standard operating procedures
- II. AFR surveillance in GLASS
  - Rationale for including AFR surveillance in GLASS
  - Potential benefits and risks of including AFR surveillance in GLASS
  - Challenges for implementing AFR surveillance at country level
  - Steps and capacity required before starting AFR surveillance
  - Selection of pathogens and antimicrobials under surveillance
  - Development of standards for internal quality assurance
  - Requirements for developing a network of reference laboratories providing support in identification and AFST

#### AMR in fungi: outputs

- Initial discussion
- Prioritize and define the way forward
- Working group?
- Resources and support needed

### *3.5.3 Group III.*

#### A. Detection of colistin resistance: questions

1. Sustainable models for colistin resistance surveillance
  - Establishment of a referral mechanism in-country
  - Recommendations on which strains should be tested, (only multi-resistant strains, carbapenemase and/or ESBL producers?) or only strains from invasive disease or as many strains as possible
- II. What technical support can be provided to countries that wish to monitor colistin resistance
  - Training to perform and interpret the tests
  - Provision of reagents and control
  - International referral of isolates

#### Detection of colistin resistance: expected outputs

- Discussion
- Outline a WHO statement
- Define next steps to develop an advice document
- Working group?

#### B. Application of molecular methods in AMR surveillance: questions

1. Surveillance on AMR and conventional molecular testing
  - How and which molecular tests can support the surveillance (epidemiologic, early detection, outbreaks) on AMR?
  - What is the best approach to include and promote molecular testing in countries participating in GLASS?

- II. What are the current approaches and experiences on molecular testing?
- TB and Rifampicin R
  - Carbapenemases in Enterobacteriaceae
  - MRSA
  - Neisseria gonorrhoeae
- III. What is in the pipeline on molecular testing and next-generation sequencing (NGS)?
- Status and future of whole genome sequencing (WGS)
  - WGS for GLASS (long term view)

Application of molecular methods in AMR surveillance: outputs

- Broad discussion
- Way forward
- Working group?
- Road map to develop the guidance on molecular testing for GLASS

**Day Two. Session Three: Group work reports**

**3.6 Group I. Emerging AMR: rapid alert and risk assessment framework**

Rapporteur: Jean Patel

The rapporteur thanked the Chair, Dr Malin Grape, for a well-organized group discussion.

*Key points*

1. Terminology and clarification
  - It was agreed that the terms “emergency”, “rapid” and “alert” were misleading in this context. Terminology should be consistent with emerging infectious disease rather than with public health emergencies. It was also recommended to avoid terms with legal or statutory implications such as notification.
  - It was also agreed that clarification was needed early in the document on the distinction and relationship between IHR reporting and AMR reporting, including a clear explanation on when each mechanism should be used.
  - It was stressed that AMR reporting should reach all constituencies that might discover new resistance, not just public health, recognizing that while some new AMR findings could represent a significant public health risk, others would not warrant an immediate response but would still be important to know.
2. Scope and target audience
  - It was noted that not all emerging AMR occurs as an outbreak and not all AMR outbreaks represent new AMR. The Risk Assessment should guide this process.
  - Response to new AMR may or may not warrant public health action, but options for action lay beyond the scope of this document.
  - The group recommended including specific examples, particularly those involving several different sectors to indicate how links should be made.
3. Provisional watch list
  - It was noted that the provisional watch list will need to be regularly and easily updated (possibly as an annex). It should not be presented as exhaustive and

should aim to be dynamic. Additional resistance to consider including: antifungal resistance; change in epidemiology; change in ecology; increase in occurrence of life-threatening infections.

4. Reporting of new AMR to GLASS

- Reporting will be via the GLASS IT platform and should be verified/confirmed by a laboratory with the necessary expertise and capacity. Reporting should be through the Ministry of Health, or if reported directly to WHO from a non-government laboratory, then WHO should inform the Ministry of Health concerned.

5. Question of incentivizing reporting

- It was noted that there is an inherent tension in reporting new AMR and withholding information for later publication purposes. To address this, journals should be encouraged to consider AMR as a public health threat and recognize reporting to GLASS of a new AMR as a citable event.
- It was also recommended to use the strongest language possible to encourage compliance without resorting to mandatory terms that implied obligation.

6. Risk Assessment

- The group recommended that the risk assessment be condensed and simplified. References to “hazards” are not relevant and should be removed, and more details specific to AMR should be included such as:
  - Frequency of resistance being reported
  - Risk of spread
  - Risk of increased mortality due to limited treatment options
  - Response needed (technical or public health intervention)
- The risk assessment process should take into account the processes for non-human health sectors, such as animals and environment, and that a more complete risk assessment may be needed to be published as a separate document.

7. Risk communication

- The section on risk communication should be expanded and should include clarification of all constituencies that should receive notification of new AMR. Support, mechanisms and tools may be needed for countries to help them develop risk communication messages. Input should be requested from FAO and OIE on the specific challenges of risk communication in their sectors (e.g. trade concerns).
- It was also noted that the document should be transparent on who has access to what levels of reported information.

*Next steps:*

The WHO GLASS secretariat will revise the document ready to be provided to Member States by April 2017. Members of the working group volunteered to help with finalization of the document, although it was noted that no representative from the environment sector was able to participate. IT capacity to report emerging AMR would be in place once Member States had approved the process as outlined in the framework.



## Discussion points

1. There was discussion on how to make horizontal intersectoral risk assessment possible in real situations when sectors work in isolation. The document recommends assembling a risk assessment team with representatives from human and animal health and the environment. i.e. multisectoral, at the national level. This will be a challenge, not just in LMICs but in all countries, but it is what needs to happen.
2. The group will identify a process in early January for completion of the draft framework by end of February/early March so that Member States will have time to consider it prior to the Member States consultation meeting in April.
3. A question was raised with regards to the level of alert for notification: Countries are expected to implement protocols for reporting new types of AMR. It will be challenging at the beginning to get everyone involved in this communication process. Experience from other rapid alert systems exist, for example influenza, indicate that buy-in within the first year was not perfect but it happened and participation was good. Thus, one can anticipate the same for AMR: there won't be complete compliance immediately but it will happen in time, with buy in from all sectors.
4. There was discussion about the level of detail to be reported. It was noted that if something new is identified, the risk assessment section of the document should help in assessing if it should be reported or not. Dr Patel felt (personally) that it is important to report if routine detection assays or phenotypic tests do not pick up the new type. But if it is just a base change that is academic rather than functional, then it does not need to be reported.
5. Information/data will it be reported on the GLASS website in the form of trends and signals captured.
6. The need for a strategy to promote the GLASS rapid alert system within the scientific community and make it more visible generally was discussed. An editorial in the Lancet or other prestigious publication, written by a technical person outside of WHO, was suggested as an example. As this is a very sensitive issue, it will require feedback from Member States. It was agreed that Members States should produce the editorial that could then be signed during the April consultation and published.

### 3.7 Group II: AMR in invasive fungi

Rapporteur Dr David Denning

Dr Denning opened by stating that the group did not consider it appropriate to include AMR in invasive fungi in GLASS at the moment.

#### *Key points*

1. Overview of the disease burden and current surveillance.

#### *A. Burden of disease categories*

(i) Hospitalized sick ICU patients – 750,000 people worldwide with invasive candidiasis, but the problem is likely to be under-estimated.

(ii) AIDS patients – very many fungal infections among AIDS patients but AMR testing is not appropriate for most. The first cases of antifungal resistance were noted in AIDS patients about 20 years ago. There is no estimate of how common it is.

(iii) Respiratory infections – e.g TB and chronic *Aspergillus* conditions e.g. severe asthma with severe fungal infections. Just under 500 000 severe asthma deaths per year with some deaths related to fungal sensitization.

*B. Surveillance:* Fluconazole resistance in all *Candida* species. Rates range from <10%-40% reflecting species mix.

2014: AMR Surveillance report indicated from 3%-5% up to >50% resistance

2015: Canada had different priorities for AMR disease threats and assessed azole resistance rates

2013: The U.S. assessed fluconazole resistance in *Candida* (all species) as a mid-tier threat

## 2. Need for a stepwise approach

The group agreed that *Candida* and *Aspergillus* should be considered by GLASS. Given the difficulties in some testing systems a stepwise approach should be taken and lessons learned from the first experiences of GLASS with bacterial pathogens.

## 3. Need for a situational analysis

A situational analysis is required: the analysis should be a combination of resistance rates and disease burden. The group agreed to try and put this together. It was noted that rates vary a lot in different countries particularly for BSI with *Candida* as species distribution is a big factor. There is also a need to understand better the situation around the clinical laboratory and epidemiology and training time implications.

The specimen for *Candida* will be blood: *Aspergillus* is primarily a respiratory specimen and therefore not within GLASS. There is a concern around testing for *Candida* resistance in the U.S. due to overlap in breakpoints between different drugs.

There is a need for more environmental surveys to assess azole resistance in *Aspergillus*. Clinical azole resistance rates are very high in the Netherlands at 16%. Resistance has also been found in people's homes. In the Netherlands, resistance is thought to be driven by the tulip bulb industry while in Britain, resistance spreads via the onion crop but is also found in other settings. Azoles are used in crop protection with five azoles being the drivers for resistance.

## 4. Approaches

Discussions have taken place between the TB/HIV/NTD Department of WHO and CDC for a focal point secondment from CDC for fungal diseases (to include AMR).

Currently, there are only three WHO CCs worldwide that address this issue: CDC in Atlanta, U.S.; an excellent laboratory in Chandigarh, India and the mycetoma centre in Khartoum, Sudan. AMR provides an opportunity for centres to collaborate with WHO and grow this area.

There is a need to increase general regional participation – CDC and perhaps the Chandigarh India centre can facilitate training to get better laboratory data sets together.

For discussion: Can *Candida* resistance rates be included in the rapid alert component? Group II requested that antifungal resistance alert criteria be developed within the group and GLASS.

## 5. Research needs

- Point prevalence studies (PPS) (like EPIC1 and EPIC2).
- Short-term cohort studies e.g. 1-month blood stream resistance study covering all pathogens in multiple centres to include *Candida*. It was clarified that these could be a complement to normal GLASS surveillance and could also complement areas of work discussed in the CC Network. They are relatively easy to do and could provide a first estimate of the burden.

There was a request for a first burden of disease estimate generated by WHO (that includes resistant *Candida*)?

- There is a need to look at oral thrush in AIDS - fluconazole is drug of choice in Africa and if there is resistance, then that is a difficult problem.
- More work on environmental *Aspergillus* is needed; this is not technically difficult but it does require training and support.
- There is a need for some fast-track incidence studies with trend analysis for *C.auris*

For the future: seven new antifungals are in clinical development. Assuming most of them get approval, at what point do they become part of the portfolio of work?

## 6. Resources

While CDC runs many prospective, multi-centre studies, national studies, some retrospective studies, lots of mapping, and will potentially provide a secondment to WHO, it was noted that the field is generally under-resourced. How can capacity in the laboratory for clinical work and for epidemiology be increased? Public health mycology is a non-existent discipline currently and needs support and expertise. It was suggested that there be a reference laboratory in each country.

Group II posed a general question for WHO and others on how to upscale this area?

## Discussion points

1. The submission of additional pathogens for surveillance reporting was discussed. Routine reporting on the eight priority pathogens is the requirement to achieve minimum global data. Despite this, some countries will struggle to provide this data while others will be doing much more than the minimum. Therefore, the expectation is that a range of data and types of feedback from GLASS-enrolled countries will be received. There will be a need to review what is provided and how to focus on priorities and acknowledge other data. Types of data will include rates and the status of development of national surveillance systems to be

reported annually (this last was requested by Member States). It is likely that some countries will not be able to report on rates at the beginning and it may take a number of years before they have the ability to do this. Attention was drawn to the “additional status” within GLASS reporting, where any extra information can be added.

It was highlighted that a rapid alert applies to any pathogen and not just the eight priority pathogens. The alert system covers both changes in epidemiology as well as new emerging resistance.

2. Criteria for reporting: It was suggested that rates of 3%-5% be used as a criteria that will trigger additional action e.g. in the case of a case of a lethal infection such as *Aspergillus* candidemia.

### **3.8 Group III: Detection of colistin resistance**

Rapporteur: Chris Oxenford

#### *Key points*

1. Guidance should not conflict with statements from CLSI/EUCAST in relation to colistin testing
2. Practically speaking, the only viable mechanism in LMICs will be via a centralized laboratory. Therefore, colistin resistance testing will be purely for surveillance, not clinical management.
3. The only validated assay is a broth microdilution so the numbers that a centralized laboratory will be able to cope with will not be large. Given this fact, the group considered different types of screening approaches. Tools that are being validated now and that could potentially be used include: selective media using disk diffusion of an as-yet-undetermined zone size; and polymerase chain reaction (PCR). It was emphasized that these should only be used as screening techniques. If resistance is found, it should then be confirmed with a validated MIC assay.
4. There was much discussion that clinical breakpoints currently in use are not of great utility. In future, epidemiological cut-offs will be used. This means that determining the zone size is still “up in the air”: interpretation is still an issue for discussion.
5. Group III felt that support should be made available to those countries that wish to acquire the ability to perform assays e.g. resources such as reference strains, and support from training institutions. This should be pursued and offered to countries who will ultimately decide if this is a priority for them or not given their very limited resources. There should be a careful discussion at country level if this is going to be taken on.

Group III will prepare more concrete guidance in the coming months.

#### **Discussion points**

1. It was acknowledged that the breakpoints used for gram-negative colistin are essentially the same as epidemiological cut-offs.

2. The meeting was urged to only recommend well-validated methods. Screening before using a validated method is a good approach but then an appropriate method should be used to avoid a false susceptibility report– the most serious error that can occur in susceptibility testing.
3. Optimism was expressed about the availability of well-performing tests coming to market in the very near future due to recent, new legislation in the U.S. that allows any breakpoint in tests for colistin susceptibility. The Microscan panel, already on the market but up to now, disallowed from advertising itself as suitable for colistin resistance testing, works well and should be more available.
4. Potential problems with the sensitivity of molecular screens were raised. There is an increasing but still inadequate understanding of the genetic basis for resistance.
5. Some meeting participants wondered about the connection of this topic to GLASS – was the point to implement worldwide testing for colistin resistance? It was clarified that one of the indicators countries are asked to report on is resistance against colistin. However, the manual does not alert countries to the difficulties of confirming one result as a true result. GLASS needs to clarify that a finding cannot be considered a final result if it is only based on disk diffusion. There is no intention to replace/duplicate what CLSI/EUCAST are doing but GLASS wants to make countries aware of the limitations of disk diffusion and give further advice. Most countries use disk diffusion but if they want to be clearer about the result, GLASS will need to guide them.

### 3.9 Group III: Application of molecular methods (MM)

Rapporteur: Matteo Zignol

Dr Zignol started by thanking the Chair, Co-Chair, note taker and all members of the working group for their lively participation and contributions to the discussion.

The objective of this working group was to develop the outline of a road map to provide guidance on molecular testing in GLASS. This would be a document to help the Collaborative Platform decide if MM could be used in GLASS and, if so, how to operationalize the use of these tools in GLASS. The contents will build on work already done by others and will likely be structured into five sections:

1. Background  
Why use molecular or genetic tests in surveillance? It is important to note that genotypic tests at this stage are complementary to cultures/AST and are not going to replace these methods. The (many) limitations of phenotypic tests need to be discussed and ways of bypassing those limitations explored. The pros and cons of the use of genotypic tests in AMR surveillance will be considered. The document will seek to capture and make sense of what is available and translate this into information that is useful for countries enrolled in GLASS. It is also important to make a distinction between molecular tests for surveillance purposes and those for diagnostic purposes.
2. What GLASS priority pathogens to target?: The intention is to explore the use of MM for surveillance, starting with the easier ones, where the science is clear and to describe resistance markers and mechanisms.

3. Laboratory methods – minimum requirements for laboratory networks: e.g. nucleotide emphasis assays such as NAATS, NGS, WGS. The aim here is to capture not just data on resistance but also information on transmission dynamics. It will be necessary to work on data interpretation: much work has already been done on this so it is not necessary to start from the beginning. What is required is to make it more usable/"digestible" so that it is useful in GLASS-supported countries. A description of bioinformatic needs and a description of the minimum requirements for laboratory networks to embark on this type of work are also needed. One laboratory in one country may not have the capacity to do everything and will need to link with other laboratories.
4. Data dissemination: this section will describe options for data reporting e.g. genotypic data, metadata. In addition, it will discuss data sharing issues. These will depend on the type of data reported with a different legal framework required for genome sequencing.
5. Operationalization and piloting: This section will include information on sourcing funds for different components e.g. consumables, maintenance, data management; how to design capacity building efforts such as education and training; IT support; developing a sustainability plan; web material; and, development of generic protocols for piloting.

### Discussion points

1. The great gulf between the reality of poorly resourced LMICs and the world of MM was acknowledged as was the need to explore avenues for GLASS to incorporate MM in the future. The application of MM is speeding up data acquisition and management of AMR surveillance. The purpose of the working group on MM is to explore the issues that will need addressing even before it will be tested in GLASS. Once that has been done, approaches to operationalization will need to be considered. The use of MM is already happening in other areas e.g. in gonorrhoea, so consideration of MM for GLASS is not so far away.
2. MM must be presented as complementary to routine GLASS activity. Otherwise, countries may devote resources to MM and neglect other methods.
3. There was a request to include chronic *Pseudomonas* within GLASS: the list of priority pathogens will be reviewed in 2019.
4. Operationalization: capacity building often translates as training but more is needed than just education and training.
5. Data dissemination is not enough; there is a need to include recommendations for action based on the data.
6. It was remarked that there is a need to consider how to package GLASS to make it more attractive and less daunting to countries. Footnotes in manuals and short explanatory attachments were recommended.
7. Epidemiological methods. Comprehensive AMR surveillance must include epidemiological methods that cover timely detection, assessment of burden, transmission dynamics, and the potential implications of AMR in healthcare. To achieve these requires representativeness to minimize bias; good coverage of populations and settings, good assessment of the context, and the ability to predict dynamics. It was suggested that GLASS needs a group to expand epidemiological methods. While not disagreeing with this, it was noted that

support to AMR surveillance is still the backbone of GLASS. The Secretariat is conscious of the need to define sentinel sites in countries and assign at least one NRL and a NCC. When it comes to the design of the surveillance strategy, generic protocols e.g. short cohorts can be used to get a sense of what is happening. It was highlighted that the Strategic Technical & Advisory Group has formally proposed that GLASS consider a global point prevalence survey on AMR. However, only 30 countries are enrolled and this is too few for a representative study. On the other hand, it could be possible to put in place surveillance strategies in low-resource settings that can be conducted in a short space of time to inform local efforts to contain AMR and that can in turn inform the global picture. Some CCs have volunteered to assist GLASS to develop protocols for this and enhance epidemiological design for meaningful information.

8. Other comments noted that it could be easier, better and more cost effective to do genotypic testing for particular types of resistance rather than building laboratory capacity. Some commercial genotypic testing systems are coming online that require relatively little hands-on training; these could potentially fit into an epidemiologically structured survey, one that can then automatically report to the cloud. This system would provide an overarching view of the data that lends itself to working out rates of resistance in particular organisms.
9. The Fleming Fund perspective on capacity development: in many low-resource settings, the key problem is lack or complete absence of basic microbiology laboratory systems. For the Fleming Fund, the priority is to help countries put in place that fundamental capacity but also that laboratory surveillance comes with clinical and epidemiological information. The priority is to help countries generate good samples/organisms with the required pedigree who can then pass these samples on to those who have the higher capacity to study the data. This is not to state that MM are not important but rather that the Fleming Fund will try and support countries to feed in to MM.
10. Data management: If genetic data is to be part of the data set, GLASS must find a way to take into account and record the relevant data. It is not clear how GLASS is proposing to handle whole genome sequences. If GLASS does not have line listing, then how will WGS work? There are a number of projects in the world in progress at the moment, and there are sure to be more, that will be global repositories for genome data. It was suggested that a relationship be made between GLASS data and these other databases and avoid duplication.
11. Clarification about new modules in GLASS: the GLASS manual, published in September 2015, committed to working on the need to capture trends and the emergence of new pathogens; to pursue the development of a module for rapid detection; and to explore the application of other technologies to enhance capacities for surveillance. The present meeting is part of the follow up to these commitments. There was acknowledgement that new GLASS modules should be identified and named clearly to avoid confusion.

## **Summary and Conclusions**

Dr Vong summarized the outcomes and next steps

### *Rapid alert protocol*

- The deadline for sharing the framework and risk assessment protocol with Member States is the end of February 2017. Dr Jean Patel, Prof Neil Woodford and Professor Roman Kozlov, with the help of Julio Pinto from FAO will do this. They will finalize the document following feedback in time for the Member States consultation at the end of April 2017.
- To inform the scientific community, the GLASS alert system will be promoted via a Lancet editorial.
- Changes to the document: the title will be changed; IHR will be differentiated from AMR and emergencies differentiated from emerging AMR; the need to share AMR information for mid-term and long-term actions will be noted.

### *Emerging AMR in fungi*

- It is too early for inclusion of this in GLASS, mostly to do with difficulties in testing. It was advised that a stepwise approach be taken and additional activities be carried out, such as a situational analysis focusing on assessing resistance rates, burden of disease, and assessing laboratory capacity throughout the world.
- There is an arrangement for CDC to second a person to WHO as a focal point for fungal infections. The limited number (3) of CCs working in this area was noted.
- GLASS will allow reporting of antifungal resistance, but criteria need to be developed. Research needs in this area include PPS, cohort studies, developing antifungal treatments. The need for funding and resources was acknowledged.

### *Detection of colistin resistance*

- There is a need for clarification on the rationale for doing this. Commercial kits are available for colistin susceptibility. Regarding issues around the difficulties of detecting colistin resistance, WHO will develop an online document explaining how to detect colistin resistance and how WHO can provide support to countries willing to undertake this testing.

### *Roadmap for guidance on MM*

- All were agreed on the importance of having molecular testing acknowledged within GLASS but as a complement to core GLASS work. The roadmap document will likely comprise five sections covering: background; the GLASS priority pathogens to target; laboratory methods and minimum requirements for laboratory networks; data dissemination; and, operationalization and piloting.
- It was noted that this was only the beginning: there is lots of work to be done to map results. There is also a need for more epidemiological analysis, better distribution and more research such as global PPS. It is also important to consider the potential impact of MM on surveillance in terms of ease, quality and cost-effectiveness versus laboratory capacity building for particular types of resistance.

## **Concluding remarks**

The development of GLASS is a shared initiative using a collaborative, consultative approach that belongs to all, not just WHO. Partners and groups will be acknowledged for their contributions. GLASS does not intend to duplicate; rather, it will align with existing initiatives and the CC Network will assist with this. Last year the Collaborative Platform recommended that GLASS improve communication via SharePoint and this has been established. The SharePoint will continue to develop as will the webpage.



The challenge now is to make GLASS grow and enhance technical support capacity. The Secretariat is very grateful to the 19 CCs who comprise the Network. The report of the Network's first meeting and the work plan for the next three years will be available on the web. CCs have a formal contract with WHO and will lead in the technical areas discussed here. The CC leads will be contacting partners for contributions in developing target products from the work plan.

While the volume of work is huge, the focus must now be on implementation. Representatives from all six WHO Regional Offices have attended this meeting as they need help with implementation and we must provide it. Special thanks were extended to the Fleming Fund for providing resources to countries for implementation and for participation in GLASS.

On behalf of the GLASS Secretariat, Dr Pessoa-Silva thanked all present for their input as did the Chair Dr Perovic who formally closed the meeting.

## Annex 1: List of participants



# World Health Organization

**2<sup>nd</sup> Meeting of the Global AMR Surveillance  
System (GLASS) Collaborative Platform  
15-16 December 2016,  
Geneva, Kempinski Hotel**

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## Annex 2: Meeting agenda



**2<sup>nd</sup> Meeting of the Global AMR Surveillance System (GLASS)**  
**Collaborative Platform, 15-16 December 2016**  
**Kempinsky Hotel**

### **Tentative Agenda**

#### **THURSDAY, 15 DECEMBER 2016**

08:30-09:00	Registration
09:00-09:10	<b>Welcome and introductions</b>
09:10-09:30	<b>Meeting format, objectives and desired outcomes</b> <ul style="list-style-type: none"> <li>• Declarations of Interest</li> <li>• Meeting rules and procedures</li> <li>• Selection of chair</li> <li>• Format and desired outcomes</li> </ul>
<b>SESSION 1: Global surveillance of AMR and AMU: an update from WHO and partners</b>	
09:30-09:40	<b>Overview of GLASS and update on early implementation</b> <i>Carmem L Pessoa-Silva (WHO)</i>
09:40-09:50	<b>Surveillance of AMR in the food chain</b> <i>Jorge Raul Matheu Alvarez (WHO)</i>
09:50-10:00	<b>Surveillance of AMU</b> <i>Arno Muller (WHO)</i>
10:00-10:10	<b>Surveillance of AMR in gonococci: update from GASP</b> <i>Theodora WI (WHO)</i>
10:10-10:20	<b>WHO initiative to foster development of new diagnostics</b> <i>Francis Moussy (WHO)</i>
10:20-10:30	<b>Discussions</b>
10:30-10:45	Coffee Break
10:45-11:05	<b>Global AMR surveillance: update from FAO</b> <i>Julio Pinto (FAO)</i>
	(15 mins presentation 5 min discussion)
<b>SESSION 2: Support to global AMR surveillance</b>	

11:05-11:25	<b>Fleming Fund initiative</b> <i>Fleming Fund representative</i>			(15 min presentation 5 min discussion)
11:25-11:45	<b>Presentation of the newly established WHO CC network and its work plan</b> TBD			
11:45-12:00	<b>Presentation of initiating group work</b> <i>Sergey Eremin (WHO)</i>			
12:00-13:00	<b>Lunch</b>			
<b>SESSION 3: AMR technical challenges</b>				
13:00-13:20	<b>GLASS Rapid Alert Component: presentation of draft protocol</b> <i>Sergey Eremin (WHO)</i>			
13:20-13:40	<b>Emerging AMR in fungi causing invasive infections in humans</b> <i>Tom Chiller (WHO Collaborating Centre)</i>			
13:40-13:55	<b>Detection of colistin resistance among <i>enterobacteriaceae</i></b> <i>Sebastien Cognat/Christopher Oxenford/Jorge Matheu (WHO)</i>			
13:55-14:15	<b>Application of molecular methods to support AMR surveillance</b> <i>Matteo Zignol (WHO)</i>			
14:15-14:30	Coffee break			
14:30-17:00	Group work: Outlining the next steps to address the surveillance challenges			
	<b>Group I:</b> Rapid Alert	<b>Group II</b> AMR in invasive fungi	<b>Group III</b> Detection of colistin resistance & Application of molecular methods	
17:00	Meeting adjourns			