Recommendations on Surveillance of Antimicrobial Resistance in Ireland

Background

This discussion document was prepared by the Antimicrobial Resistance (AMR) Surveillance Working Group, one of a number of working groups set up as part of the Strategy for the control of Antimicrobial Resistance in Ireland (SARI). The working groups were set up to develop recommendations on specific areas within SARI and are made up of representatives from relevant professional bodies. The working groups report to the SARI National Committee, which is based at the Department of Health and Children (DOHC). The membership of the SARI AMR Surveillance Working Group is listed at the end of this document.

This discussion document considers current and future requirements for AMR surveillance in Ireland and lists a series of draft recommendations to be distributed for broad consultation.

Summary of draft recommendations

1. AMR surveillance programmes should follow the objectives and general principals set out in the World Health Organisation document "Surveillance standards for antimicrobial resistance"

The principal purpose of AMR surveillance data is to optimise antimicrobial use, inform strategies for the prevention, control and containment of AMR at local, regional and national levels and monitor the impact of such strategies.

The following list of desirable features for surveillance systems are adapted from the WHO document "Surveillance Standards for Antimicrobial Resistance":

- Surveillance should be focused on microorganisms or infectious agents of greatest public health importance (i.e. with high mortality and/or morbidity, and/or where therapeutic options may be severely limited by antimicrobial resistance)
- Surveillance systems should include microorganisms or infectious agents that are readily transmissible (i.e. may give rise to outbreaks and epidemics)
- Surveillance systems should provide information on mortality and morbidity attributable to resistant strains of the organism in the context of that attributable to susceptible strains (i.e. be integrated with communicable disease surveillance systems)
- Surveillance systems should provide information for action at the local, intermediate and national levels.
- Participation at the local level should be made as easy as possible. Data provision should fit as closely as possible with routine practice and minimise additional workload.

- Systems should capture the minimum amount of data needed for useful surveillance and an evidence-based approach to public health interventions.
- Data on antimicrobial resistance should be of a consistently appropriate quality. Antimicrobial susceptibility testing should be carried out using standardised methodologies and subject to internal and external quality control.
- The capture, collation and analysis of data should be in accordance with protocols of appropriate quality, such as those laid out in *WHO Recommended Surveillance Standards*, including:
    - Clear, appropriate, consistent case definitions
    - Clear, efficient reporting mechanisms
    - Appropriate, timely data analysis and feedback
    - Sufficient human and material resources
- Information outputs should facilitate decision-making by clear presentation and timely distribution, and should include a commentary on the limitations of the data presented as well as proposals for interventions.

The decision to undertake the surveillance of and microbiological testing of pathogens for antimicrobial resistance will be determined, in part, by the extent to which resistance impacts on therapy. Establishment of surveillance systems is essential for improving appropriate antimicrobial use and containing the threat of antimicrobial resistance.

2. AMR surveillance should include appropriate denominator data

Laboratory specimens or isolates are often used as denominators in AMR surveillance, as is the case with European Antimicrobial Resistance Surveillance System (EARSS). For example methicillin resistance in *Staphylococcus aureus* is expressed as a percentage of total *S. aureus* blood culture isolates. Such percentage resistance levels are useful for comparing the prevalence of resistance in specific pathogens between countries, but are less useful for national or regional AMR surveillance. Criteria for submission of microbiological specimens for analysis are generally subjective and inconsistent and vary widely between different specimen types, patient groups, clinicians and laboratories. Percentage resistance levels may overestimate the true prevalence of resistance, particularly if specimens are only submitted from the sickest patients or from those in whom previous antimicrobial therapy has failed. Likewise percentage resistance does not give any indication of the disease burden resulting from AMR: estimation of disease burden is important for planning interventions to control AMR.

Percentage resistance levels may be useful for local AMR surveillance, where specimen submission and local laboratory protocols are likely to be relatively consistent over time. Such levels are most useful in the setting of AMR prevalence studies where specimens are submitted and analysed according to agreed protocols, such as the proposed prevalence study of community-acquired urinary tract infection detailed below. It is in this setting that percentage resistance can best be used to guide empiric prescribing for common infections.

Wherever possible AMR rates should be expressed in terms of cases within a defined population for a given time period: e.g. quarterly methicillin-resistant *S. aureus*

(MRSA) bacteraemia per 1000 hospital discharges or quarterly quinolone-resistant *Salmonella* infections per 100,000 population. Such rates give an indication of the local disease burden resulting from AMR.

It is important that such rates are stratified to control for confounding variables, such as patient age, severity of disease on admission, bed occupancy, hospital activity etc. This will allow more meaningful comparison of AMR data between institutions and regions over time, though even with control for confounding variables comparisons in rates of infection between institutions are problematic. The primary goal is to produce meaningful analyses that allow institutions to monitor their local AMR prevalence over time and identify emerging problems.

3. All diagnostic microbiology laboratories should participate in the European Antimicrobial Resistance Surveillance System (EARSS)

Susceptibility data on invasive isolates of *S. aureus*, *Escherichia coli*, *Streptococcus pneumoniae* and enterococci (*E. faecium* and *E. faecalis*) are gathered from participating laboratories in a number of European countries, including Ireland. Data are analysed on a quarterly basis, and are restricted to the first isolate per quarter on each patient. In Ireland, 25 laboratories currently participate in EARSS, covering 85-90% of the population, and further laboratories are due to participate. MRSA isolates are referred for reference susceptibility testing and typing to the MRSA reference laboratory, based at St. James' Hospital in Dublin.

The data generated by EARSS has been extremely valuable in determining the scale of antimicrobial resistance in Ireland and has the advantage that resistance data can be compared between European countries. There are some disadvantages, however, to the EARSS system. The major disadvantage is that data are only available on invasive isolates that, particularly in the case of *S. pneumoniae*, may underestimate the overall level of resistance. There are also selection biases in restricting the data to invasive isolates. Data is only available on patients who have had blood cultures taken. Thus only the sickest patients are represented and local blood culture policies may impact on patient selection. Most of the isolates reported to EARSS represent hospital-acquired infections, though antibiotic resistance in *S. pneumoniae* primarily reflects community antibiotic use.

Despite these shortcomings EARSS has proven a very valuable surveillance system and should serve as a model for development of future surveillance programmes.

Automated downloading of EARSS data from laboratory information systems can easily be achieved using WHONET software, which is already in place in a number of participating laboratories. Surveillance of EARSS pathogens will also be included in CIDR. Such automation results in minimal additional workload for participating laboratories.

Participation of all diagnostic laboratories would mean that accurate population-based infection rates could be determined (e.g. enterococcal bacteraemia per 100,000 population per quarter). Full participation would also allow greater stratification of EARSS data, to allow meaningful inter-regional and inter-institutional comparisons.

4. AMR surveillance based on routine laboratory data should be based on EARSS methodology

Surveillance of AMR in any additional pathogens at regional or national level should be based on the EARSS model. Laboratory experience with EARSS, along with existing software protocols for obtaining data on current EARSS pathogens, would minimise the additional laboratory workload associated with adding any additional pathogens.

The key components of any such additional surveillance would include:

- Restricting surveillance to targeted pathogens and specimens
- Restricting susceptibility data to a small number of routinely tested, clinically important antimicrobials (3-5 agents)
- Only reporting the first isolate per patient per quarter

One option would be to carry out surveillance of all bloodstream isolates, similar to current bacteraemia surveillance in the UK. Such surveillance would require automated downloading of data from laboratory information systems. A pilot study is proposed for a small number of laboratories using WHONET/BACLINK software to assess the feasibility of such surveillance, additional laboratory workload and the surveillance value of the collected data.

5. National AMR surveillance should be based on targeted surveillance of key pathogens

Some AMR surveillance systems collect most or all routinely generated susceptibility data produced by participating laboratories. One example of this is The Surveillance Network (TSN) in North America. Automated surveillance of all routinely generated susceptibility data has a number of advantages. Firstly little or no additional workload is required on the part of participating laboratories, other than installation and maintenance of software linked to the laboratory information system. Secondly the data is already being generated and, in most laboratories, is available in electronic format. Thirdly there are a number of support systems, such as RGSD (UK PHLS software programme) and WHONET, already available to facilitate the collection of routine susceptibility data.

However the comprehensive collection of routine susceptibility data has a number of disadvantages. Numerous selection biases impact on data quality: susceptibility tests are not performed on all isolates, not all isolates are fully identified and susceptibility test methods may differ between laboratories. Likewise susceptibility-testing panels differ between laboratories and between different specimen types within individual laboratories. Collection of all routinely generated susceptibility data does not distinguish between colonisation and infection and there is likely to be over-representation of certain hospital areas, such as intensive care units. Multiple isolates from the same patient are also likely to skew the data towards an over-estimation of resistance levels.

For the purposes of national AMR surveillance a targeted approach should be used, similar to the current EARSS protocol. This allows more meaningful interpretation of data to be made between different regions and over time. A list of possible priority organisms/infections for national AMR surveillance is given in the table at the end of this document. Additional organisms/infections may be targeted for local or regional surveillance in response to local problems (e.g. increased prevalence of specific hospital-associated Gram negative bacilli).

6. National AMR surveillance should be based on a minimal core dataset

One of the key principals of disease surveillance is to collect the minimum data necessary, rather than the maximum data possible. Collection of a minimal core dataset minimises the workload for data providers and facilitates uniform data collection and reporting. The core data set for national AMR surveillance, for a given pathogen, might include:

- Organism name
- Susceptibility results (3-5 key antimicrobials)
- Patient age
- Patient sex
- Date culture taken
- Date of admission, if available
- Hospital location (ICU, casualty etc.), if available

Additional data may be collected as part of local or regional surveillance programmes, such as additional clinical details, recent antibiotic use, previous hospital admissions etc. Participating laboratories would report the core data set to regional and national SARI committees, with additional locally-agreed data reported to the regional committee.

7. Specific laboratory resources will need to be in place to facilitate comprehensive AMR surveillance

The level of participation in EARSS by Irish laboratories is very high, compared to other European countries, despite the frequent lack of resources and considerable routine workload of Irish diagnostic laboratories. While minimal additional AMR surveillance may be possible with current resources comprehensive local, regional and national AMR surveillance will require additional resources. Specifically the AMR surveillance working group has identified three key resources that need to be in place in diagnostic laboratories:

- Electronic data collection
- Standardised susceptibility testing
- Laboratory surveillance personnel

Electronic data collection

Manual collection and reporting of AMR data is only practicable where an individual laboratory is reporting a small number of pathogens. With additional pathogens included in AMR surveillance manual data collection will be excessively labour-

intensive. Thus some form of electronic data collection is essential for comprehensive AMR surveillance.

The introduction of CIDR will provide a uniform electronic data collection system for all diagnostic laboratories. AMR surveillance has been identified as one of the key components of CIDR and a module for automated reporting to EARSS has been developed. In addition CIDR will allow comprehensive, automated collection of AMR data on notifiable pathogens, such as *Campylobacter spp., Neisseria gonnorhoeae* etc.

There will be some delay before CIDR is in place in all diagnostic laboratories. In addition CIDR is not suitable for collection of large volumes of AMR data from non-notifiable pathogens. For these reasons additional options for electronic data collection need to be considered, particularly for any comprehensive local or regional AMR surveillance needs. WHONET software is specifically designed for automated collection of routine susceptibility data and, when combined with BACLINK software, can download data automatically from laboratory information systems. WHONET is already in use in a number of Irish laboratories participating in EARSS and there is ongoing support for its use through WHO. It is likely that WHONET will be used as the primary means of electronic AMR data collection, pending the introduction of CIDR. WHONET will also complement data collection through CIDR, particularly for local analysis of susceptibility data, once the latter system is in place.

Standardised susceptibility testing

The Irish Society of Clinical Microbiologists and the Academy of Medical Laboratory Science have recently recommended that all Irish diagnostic laboratories use the standardised susceptibility testing protocols developed by the US National Committee for Clinical Laboratory Standards (NCCLS). NCCLS methodologies are widely used across Europe and North America. The introduction of a standardised method, used by all Irish laboratories, will mean that routine AMR data will be more consistent between participating laboratories, as well as allowing more meaningful comparison of Irish data with data from other European countries. In addition NCCLS methodology includes a number of internal quality controls for susceptibility testing.

Under NCCLS disc diffusion methodology antimicrobial susceptibility data can be quantified, by reporting the diameter of the zone of inhibition of growth to an antimicrobial agent on susceptibility plates. The measured zone diameter is used as a basis for categorising the isolated for clinical purposes as susceptible (likely to respond to treatment), intermediate (may respond under certain circumstances) or resistant (unlikely to respond to treatment). Reporting of the measured zone diameters for AMR surveillance is preferable to reporting only the interpretive category (i.e. sensitive, intermediate or resistant) derived from the measurement. If surveillance is based solely on susceptibility test categories, rather than on the measured values there is a loss of significant detail. Reporting of zone diameters allows for more accurate assessment of AMR trends, particularly the potential emergence of new resistance problems.

This can be illustrated with reference to the example of ciprofloxacin. With the standard ciprofloxacin containing disk most *E. coli* have very large zone diameter

(>35 mm in most cases) however all isolates with a zone diameter of >= 17mm are in the category of susceptible although it is now apparent that isolates with a zone diameter of 20mm may already have an important mutation that brings them half way towards outright resistance to ciprofloxacin. Treating all isolates with a zone diameter of >=17mm (susceptible) as indistinguishable for surveillance purposes means that gradual stepwise reductions in zone diameter over time would go unnoticed and a potential emerging resistance threat would be missed.

Surveillance personnel

The SARI report recommended that each diagnostic laboratory should have a designated member of staff with responsibility for surveillance. In most instances this will be a surveillance scientist. Larger hospital laboratories will require a full-time surveillance scientist, while smaller laboratories will probably only require a half-time equivalent. A number of laboratory surveillance scientist appointments have already been made but it is imperative that all diagnostic laboratories have sufficient staffing for surveillance activities.

8. Periodic prevalence studies should be used to determine resistance levels among key community-acquired pathogens

The selection biases associated with using data from routinely submitted laboratory specimens may be particularly marked with community-acquired infections. Most antimicrobial prescribing in the community is empiric and laboratory specimens are often only submitted on the sickest patients, those at extremes of age and those who have failed previous antimicrobial therapy. Thus resistance levels may be overestimated.

There is a need to identify what are the most frequent pathogens causing common community-acquired infections and establish regional susceptibility profiles. The two infections accounting for most empiric prescribing in the community are respiratory tract infections and urinary tract infections. Establishing reliable susceptibility data to inform empiric prescribing for these infections can only be achieved through targeted prevalence studies. In such studies specimens from a pre-defined number of patients fitting an agreed case definition are sent from a geographically representative sample of general practices over a given time period. For example, in the case of urinary tract infections, general practitioners may be asked to submit an MSU sample on the first five women aged 18-65 presenting with symptoms fitting an agreed case definition of cystitis and who have received no antimicrobial therapy in the previous three months, during a given two week period. Causative organisms would be identified to species level and tested against an agreed range of antimicrobials. Laboratory testing could either be carried out in local laboratories or in one designated laboratory. Where testing is performed in a local laboratory there is a requirement for a proportion of isolates or for isolates with unusual resistance phenotypes to be validated by a central reference laboratory.

Such prevalence studies will need to be repeated at regular intervals and be of sufficient size to allow regional analysis of trends in susceptibility. Additional funding will be required to carry out such studies.

9. Reference laboratory support will be required for effective AMR surveillance

Reference laboratory support for AMR surveillance is identified as a key requirement in the both the SARI report and the WHO strategy for control of antimicrobial resistance. A priority list of reference laboratory services needs to be developed, with reference laboratory support for AMR surveillance included as an essential component.

The value of reference facilities, not just for AMR surveillance, has been demonstrated by the work of current national reference laboratories for meningococci, MRSA and *Salmonella enterica*. Additional reference facilities are required to support AMR surveillance of key pathogens, particularly *Streptococcus pneumoniae*, enterococci, *E. coli* and other Gram-negative pathogens. Reference laboratory support is important not only for validation of resistance of specific isolates but also to support the maintenance of highest standards of susceptibility testing in routine diagnostic laboratories. A reference laboratory should assist diagnostic laboratories with ongoing training, and quality improvement and also work to disseminate and understanding of the problem of antimicrobial resistance more widely in the health care sector and among the general public. The introduction of NCCLS methodology to diagnostic laboratories in recent years has highlighted the need for leadership and guidance for diagnostic laboratories. Reference laboratories are an important source of such expertise.

One option for reference laboratory services for AMR surveillance would be to have a "virtual reference laboratory". Rather than having a single large AMR laboratory individual services would be provided by separate, cooperating laboratories using agreed methods for susceptibility testing and data collection. This is similar to the model proposed for food safety reference laboratory facilities. A steering group, made up of the directors of the individual laboratories, would coordinate AMR services between the participating laboratories.

10: Human AMR surveillance should be linked to AMR surveillance of pathogens of non-human origin

About half of all antimicrobial use occurs in animal husbandry and other areas of agriculture. Antimicrobial use in agriculture may impact human health through antimicrobial residues in food products, environmental transfer of genetic AMR determinants or antimicrobial resistance in zoonotic pathogens. Examples of the latter include quinolone resistance in *Salmonella enterica* and *Campylobacter spp.* and vancomycin resistance in some enterococci linked to agricultural quinolone and glycopeptide use respectively.

While SARI focuses on the control of AMR in humans there is a need to establish links with AMR control programmes in agriculture and food production, including

surveillance of AMR in zoonotic pathogens. AMR data on notifiable pathogens, such as *Salmonella enterica* and *Campylobacter spp.* will be collected as part of CIDR, though this data will be restricted to human isolates. Other data sources for AMR in pathogens of animal origin include the National Salmonella Reference Laboratory and the Central Veterinary Research Laboratory. AMR data may also become available from the proposed food safety reference laboratory facility or from other reference facilities in the future.

Consideration should also be given to surveillance of AMR in microorganisms isolated from water, sewage or other environmental sources, which may act as a marker of overall AMR in human or animal populations or as a predictor of emerging AMR threats.

Working group membership

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Draft List of Priority Organisms for AMR Surveillance

Organism	Protocol(s)	Anatomical site	Patient source	Antibiotics tested for surveillance purposes*	Comments
*Streptococcus pneumoniae***	EARSS	Blood, CSF	In-patients	Penicillin, 3rd generation cephalosporins, macrolides, quinolones	Resistance primarily reflects community antibiotic use. Linkage of resistance levels to pneumococcal serotype recommended by WHO, to inform vaccination strategies.
*Staphylococcus aureus***	EARSS	Blood	In-patients	Methicillin/oxacillin, vancomycin, ciprofloxacin, erythromycin, gentamicin	Methicillin resistance levels primarily reflect hospital activity. Additional data provided by National MRSA Reference Laboratory
*Escherichia coli **	EARSS	Blood	In-patients	Ampicillin, 3rd generation cephalosporins, ciprofloxacin, gentamicin	Screening for extended spectrum beta-lactamase production also included in protocol
Enterococci: *E. faecalis, E. faecium*	EARSS	Blood	In-patients	Ampicillin, gentamicin, vancomycin	High-level gentamicin resistance and vancomycin resistance
Gram-negative hospital pathogens: *Pseudomonas aeruginosa, Klebsiella pneumoniae***	EARSS-based	Blood/sterile sites, urine	In-patients	3rd generation cephalosporins, gentamicin, ciprofloxacin, carbapenems	Other potential pathogens in this group include *Enterobacter spp., Serratia spp., Acinetobacter spp* etc.
*Haemophilus influenzae, S. pneumoniae***	Prevalence survey	Sputum, nasopharyngeal swabs	Out-patient	Penicillin, ampicillin, erythromycin, trimethoprim, tetracycline	Annual prevalence survey during winter months. Nasopharyngeal swabs for children.
Streptococcus pyogenes	Prevalence survey	Throat	Out-patient	Erythromycin, tetracycline	Periodic survey of results from routinely-submitted specimens may suffice

Organism	Protocol(s)	Anatomical site	Patient source	Antibiotics tested for surveillance purposes*	Comments
Urinary pathogens (*E. coli, Klebsiella spp., Proteus spp., Staphylococcus saprophyticus,* enterococci, etc.	Prevalence survey	Urine	Out-patient	Ampicillin, gentamicin, co-amoxiclav, ciprofloxacin, trimethoprim,	Annual prevalence survey, probably during summer months.
All blood culture isolates	Modified EARSS protocol	Blood	In-patient	Summary report of most commonly tested agents	Based on automated download of first blood culture isolate per patient per quarter from laboratory information systems
*Neisseria gonorrhoeae***	Notifiable pathogen	All clinical isolates	In-patient and out-patient	Penicillin, tetracycline, 3rd generation cephalosporin, ciprofloxacin	
*Neisseria meningitidis***	Notifiable pathogen	Blood, CSF	In-patient	Penicillin	
Salmonella enterica	Notifiable pathogens	All clinical isolates	In-patient and out-patient	Ampicillin, chloraphenicol, cotrimoxazole, 3rd generation cephalosporin, ciprofloxacin	

*Antibiotics are selected to represent class resistance
**Key pathogens listed in WHO Surveillance Standards for Antimicrobial Resistance. Remaining pathogens on WHO recommended list are *Salmonella enterica* serotype Typhi and *Shigella dysenteriae*, both of which are included within the list of notifiable pathogens in Ireland.