Integrated Surveillance of Antimicrobial Resistance

Guidance from a WHO Advisory Group

World Health Organization

AGISAR

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Preamble

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was established in December 2008 to support WHO's effort to minimize the public health impact of antimicrobial resistance (AMR) associated with the use of antimicrobials in food animals. The Group comprises over 30 internationally renowned experts in a broad range of disciplines relevant to antimicrobial resistance, appointed following a Web-published call for advisers, and a transparent selection process. The terms of reference of the WHO AGISAR are given below.

- Develop harmonized schemes for monitoring antimicrobial resistance in zoonotic and enteric bacteria.
- Support WHO capacity-building activities in Member countries for antimicrobial resistance monitoring (AMR training modules for Global Foodborne Infections Network (GFN) training courses).
- Support WHO capacity-building activities in Member countries for antimicrobial usage monitoring.
- Update the WHO list of Critically Important Antimicrobials for Human Medicine.
- Provide expert advice to WHO on containment of antimicrobial resistance with a particular focus on critically important antimicrobials.
- Support and advise WHO on the selection of sentinel sites and the design of pilot projects for conducting integrated surveillance of antimicrobial resistance.
- Promote sharing of information on AMR.

The WHO AGISAR holds regular telephone conferences and annual face-to-face meetings. During its first meeting in June 2009 in Copenhagen, Denmark, the Group acknowledged the existence of differences in proficiency in programmes monitoring antimicrobial resistance in foodborne and zoonotic bacteria, and developed a five-year strategic framework to address this.

The present guidance document is an important output of the five-year strategy. It has been developed through a four-year consultative process including teleconferences and face-to-face meetings. The guidance was finalized during the fourth annual meeting of the WHO AGISAR in Aix-en-Provence, France, on 24-25 June 2012. It is intended to provide WHO Member States with key information on designing a programme for integrated surveillance of antimicrobial resistance.

Declaration of interest

All experts and resource advisers invited to participate in the Expert Consultations completed the WHO standard form for declaration of interests prior to the meeting. At the start of the meeting, all participants were asked to confirm their interests, and to provide any additional information, relevant to the subject matter of the meeting. No conflicts of interest were identified.

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[1] The Food and Agriculture Organization of the United Nations, the World Organisation for Animal Health, the European Centre for Disease Prevention and Control and the European Food Safety Authority.

Acronyms and abbreviations used in this document

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AGP	antimicrobial growth promoter
AMR	antimicrobial resistance
ATC	anatomical therapeutic chemical
CIA	critically important antimicrobial
CLSI	Clinical and Laboratory Standards Institute
CSF	cerebrospinal fluid
DCDD	defined course dose animals
DDD	daily defined dose
DDDA	daily defined dose animals
DOT	days on therapy
ECDC	European Centre for Disease Prevention and Control
ECOFF	epidemiological cut-off value
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EQAS	External Quality Assurance System
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	extended spectrum beta-lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization of the United Nations
GFN	Global Foodborne Infections Network
INRUD	International Network for Rational Use of Drugs
ISO	International Organization for Standardization
MIC	minimum inhibitory concentration
MLST	multi-locus sequence typing
OIE	World Organisation for Animal Health
PCR	polymerase chain reaction

PCU	population correction unit
PFGE	pulsed-field gel electrophoresis
PPS	point prevalence study (survey)
QC	quality control
RIS	resistant, intermediate, sensitive
WHO	World Health Organization

Executive summary

Despite several international recommendations during the last two decades harmonized surveillance for antimicrobial resistance have still not been established worldwide. Differences in production systems, sampling sites and procedures, as well as antimicrobial agents tested for makes comparison between countries difficult and even at times impossible. Today continuous surveillance programs for antimicrobial resistance, where data to some extend can be compared, only exist in most of the EU-countries, USA, and Canada.

Integrated surveillance of antimicrobial resistance in foodborne bacteria is the coordinated sampling and testing of bacteria from food animals, foods, and clinically ill humans, and the subsequent evaluation of antimicrobial resistance trends throughout the food production and supply chain using harmonized methods. Global harmonization of integrated surveillance programmes is needed so that surveillance data from different areas, countries and regions can be more easily compared. A major impediment to such harmonization is the lack of uniform standards and policies in sampling, testing and reporting.

WHO has recommended that countries develop antimicrobial surveillance programmes that integrate data from bacterial isolates originating from humans, food-producing animals, and retail meats. The rationale of integrated surveillance is to detect the emergence and spread of resistant bacteria that may cause foodborne disease. The Codex Guidelines on Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77-2011) also emphasized the importance of programmes for surveillance of use of antimicrobial agents and prevalence of foodborne antimicrobial resistance as important sources of information needed for risk analysis.

This guidance document provides the basic information that countries need to establish a programme for integrated surveillance of antimicrobial resistance, taking a step-by-step approach to designing the programme and using standardized and validated antimicrobial susceptibility testing methods and harmonized interpretative criteria.

Section 1 provides guidance on surveillance and monitoring approaches, including minimum requirements for an integrated monitoring system. It also outlines the sampling strategies and laboratory standards that need to be applied. Data analysis and reporting methods are provided to permit national and international comparison of findings.

Data from surveillance of the consumption of antimicrobial agents in humans and animals can be integrated with antimicrobial resistance data to identify trends, evaluate interventions and support

risk analysis. Sections 2, 3 and 4 aim to support and promote the collection of standardized data on the usage of antimicrobial agents in humans and animals, including farmed fish, at regional and national levels.

The strength of any surveillance programme depends on its data management system. Sections 5 and 6 provide guidance on data management systems to support integrated surveillance of antimicrobial resistance and antimicrobial consumption, and describe existing software resources.

Finally, as surveillance activities generate information of interest to multiple stakeholders, specific tools and strategies will be required to provide appropriate information without triggering an over-reaction. Guidance is provided in section 7 on effective risk communication on antimicrobial resistance.

Integrated surveillance of antimicrobial resistance in foodborne bacteria

1.1 Scope

Integrated surveillance of antimicrobial resistance (AMR) in foodborne bacteria is the coordinated sampling and testing of bacteria from food animals, foods, and clinically ill humans, and the subsequent evaluation of antimicrobial resistance trends throughout the food production and supply chain using harmonized methods. Global harmonization of integrated surveillance programmes is needed so that surveillance data from different areas, countries and regions can be more easily compared. A major impediment to such harmonization is the lack of uniform standards and policies in sampling, testing and reporting. Harmonization does not mean that all programmes conduct their activities in exactly the same way. Local epidemiology and treatment of foodborne diseases, public health resources, laboratory capacity, government policies, production practices, food animal processing, distribution of food products, and pre-existing public health infrastructure all influence the design of national monitoring programmes. Where programmes cannot be changed, a clear description of the sampling and testing methods should be provided, so that the strengths and limitations of programmes can be compared.

This document aims to promote programme compatibility, so that monitoring is conducted and results are reported in a comparable fashion. To do so, it:

- provides guidance on surveillance and monitoring approaches, including minimum requirements for integrated monitoring systems;
- provides guidance on sampling strategies;
- sets out guidelines and standards for laboratory culture, bacterial identification, antimicrobial susceptibility testing methods and quality assurance;
- proposes analysis and reporting methods that allow findings to be compared within and between countries;
- makes recommendations for international harmonization of integrated antimicrobial resistance monitoring systems for foodborne bacteria, including both pathogenic and commensal organisms.

1.2 Purpose of antimicrobial resistance monitoring

While monitoring for the development of antimicrobial resistance in humans has been carried out since antimicrobials first became widely available, it was initially usually limited to local programmes designed to guide patient therapy. As resistance to new antimicrobials emerged, and multiple drug

resistance developed and spread, the need for comprehensive surveillance systems for antimicrobial resistance was recognized as a public health priority throughout the world.

The monitoring of resistance in foodborne bacteria requires an integrated approach using harmonized methods. In 2000, a WHO report recommended that countries develop antimicrobial resistance surveillance programmes that integrate data from bacterial isolates originating from patients, food-producing animals and, where appropriate, retail meats (1). The World Organisation for Animal Health (OIE) has developed standards on this subject, which are published in the Terrestrial Animal Health Code (2) and the Aquatic Animal Health Code (3). This type of surveillance monitors the emergence and spread of resistant bacteria in animal products and other foods destined for human consumption. The extensive and increasing global trade in food animals and their derived commodities highlights the growing importance of global data-sharing on foodborne pathogens and disease.

An antimicrobial resistance surveillance system for bacteria commonly transmitted by food should provide data that can be used to:

- document the levels of antimicrobial resistance in different reservoirs;
- identify trends over time and from place to place in antimicrobial resistance;
- describe the spread of resistant bacterial strains and genetic determinants of resistance;
- clarify the association between antimicrobial resistance and use of antimicrobial agents;
- generate hypotheses about sources and reservoirs of resistant bacteria;
- identify appropriate interventions to contain the emergence and spread of resistant bacteria and evaluate their effectiveness;
- develop targeted epidemiological and microbiological research for source attribution studies, and identify risk factors and clinical outcomes of infections caused by resistant bacteria;
- inform risk analysis of foodborne antimicrobial resistance hazards;
- guide evidence-based policies and guidelines to control antimicrobial use in hospitals, communities, agriculture, aquaculture, and veterinary medicine;
- deliver education on current and emerging hazards.

1.3 Minimum requirements for surveillance

The design of antimicrobial surveillance programmes presents several challenges. Not all countries have the same public health infrastructure, and it is important to establish a minimum set of criteria for surveillance systems. A surveillance system should be set up only if there is a recognized public

health burden of enteric illness due to a specific foodborne etiological agent. If this is the case, the most important prerequisites for an effective system include:

- an adequate health care infrastructure that allows clinical specimens to be properly collected and microbiological culture to be performed as part of routine patient care;
- food consumption data, to establish the sampling design and prioritize pathogens, animals and foods to be tested;
- established laboratory facilities and trained personnel; and
- capacity to capture, analyse and report surveillance data.

In addition, a surveillance programme must be sustainable over time, to provide the data needed to establish trends in antimicrobial resistance for public health decision-making. The participation of different sectors and disciplines is essential to sustain programmes for the long term. Scientists from different disciplines (e.g. physicians, veterinarians, microbiologists, epidemiologists and soil scientists), and representatives from food production industries, as well as government agencies responsible for risk assessment, risk management and research, have a role in supporting and sustaining an integrated surveillance system.

A sustainable integrated antimicrobial resistance surveillance programme requires the following:

- a sound sampling scheme along the food chain;
- sustained political and financial support arising from a recognition of the public health importance of surveillance;
- ongoing quantitative and qualitative risk assessments for emerging and potential hazards and the flexibility to adjust resources and programme priorities as necessary;
- cooperation and good communication between the agriculture and public health sectors;
- collaboration and information-sharing between microbiologists, clinicians, epidemiologists, veterinarians, food scientists, food producers and public health officials within and across sectors;
- microbiological and epidemiological research to better understand the implications of data from routine monitoring;
- publication of findings for different audiences in a timely manner;
- a continuous process of programme review and enhancement.

1.4 Elements of an integrated antimicrobial resistance surveillance system

The following issues need to be considered when an integrated surveillance system is being established:

- **sample sources**

- humans,
- retail foods,
- food-producing animals;

- **target microorganisms**

- major foodborne pathogens,
- sentinel organisms,
- other bacteria;

- **sampling design**

- sample source,
- sample information,
- sampling representativeness,
- collection frequency,
- sample size;

- **laboratory testing methodology**

- bacterial culture methods,
- storage of bacterial isolates,
- identification of isolates,
- standardized antimicrobial susceptibility testing and quality control,
- recommended antimicrobials for surveillance;
-

- **data analysis and reporting**

- programme description,
- data interpretation,
- data presentation.

The ways in which data are captured, analysed and published are key to informed public health decision-making.

1.5 Sample sources

For integrated surveillance, a three-part approach that includes bacteria from human clinical cases, food animals (sick and healthy), and animal-derived food products is optimal. Isolates from all sources should be tested using recognized methods and comparable antimicrobial arrays, and data made available for comparison with data on human isolates. Monitoring can be implemented incrementally or limited to priority study populations, or sources and organisms may be alternated over time. The guidance below is offered to help prioritize surveillance components.

1.5.1 Human isolates

The first priority is to monitor bacterial isolates from clinical cases of foodborne illness in humans. Such isolates may be acquired from institutes with laboratory capacity for routine clinical testing, including health care facilities and outpatient clinics, and should include representative strains from sporadic and outbreak cases. It is important to distinguish hospital-acquired infections from community-onset infections if possible. Expanded human sampling strategies can include selected subpopulations (e.g. the elderly, young people and healthy carriers).

Most foodborne illness in humans involves intestinal infection, and a subset of these cases will be sufficient for representative monitoring purposes. Because extra-intestinal infections are associated with higher morbidity and mortality, it is desirable to test as many of these as possible.

1.5.2 Retail food isolates

For countries that are starting a surveillance programme, retail foods of animal origin are the second priority for monitoring, since these represent the major route of human exposure. The selection of foods for surveillance (beef, chicken, turkey, pork, fish, lamb, etc.) should reflect consumption patterns in the population, but may be modified from year to year in order to capture multiple commodities. Food samples should be collected in a manner that reflects the purchasing habits of the consumer (e.g. in open markets or chain stores). The statistical database of the Food and Agriculture Organization of the United Nations (FAO) (4) summarizes consumption data for different countries, and is a useful source of information to help determine priorities.

1.5.3 Food-producing animals

Samples from food animal sources would be the third step in programme expansion. Samples should be taken from animal species corresponding to the retail meats under surveillance. If on-farm sampling is not possible, samples from healthy animals at slaughter may be used to estimate bacterial resistance in food animals. Animal sampling poses particular challenges that are discussed further in section 1.7.

1.6 Target organisms

The selection of bacterial pathogens to be included in antimicrobial susceptibility monitoring depends on local public health priorities, antimicrobial use practices and the local burden of foodborne illness.

1.6.1 Major foodborne pathogens

Because *Salmonella* is a major foodborne pathogen around the globe, it is the first priority for testing. *Campylobacter* spp. are also important foodborne pathogens, and are included in many national surveillance schemes. *Campylobacter* may not be a priority in some developing countries, where other foodborne organisms, such as *E. coli*, may be a higher priority.

1.6.2 Sentinel organisms

Salmonella and other pathogens will not be found in every meat or animal sample. Because *E. coli* is common and some strain variants may cause disease, it can be used as a sentinel organism for antimicrobial selection pressure. *E. coli* and *Enterococcus* also serve as reservoirs of resistance genes that can be transferred to overt human pathogens transiting the intestinal tract; as such, they provide information on the flow of Gram-positive and Gram-negative resistance traits in the food chain.

1.6.3 Other bacteria

The choice of other bacteria depends on the epidemiology of foodborne diseases in the area, which may change over time. In addition to the major pathogens already mentioned, other veterinary or human bacteria, e.g. *Staphylococcus* and *Clostridium*, may be relevant, including those associated with aquaculture, e.g. *Vibrio*.

1.7 Sampling design

Sampling design has a major impact on the reliability of inferences that can be drawn from the data; a sound design is crucial to any surveillance programme.

1.7.1. Sample source

For human and food sources of bacteria, it is relatively straightforward to accommodate possible biases associated with the sample source. For food animals, there are many potential sampling points in the production and processing continuum, and different information will be obtained at different points. When reporting surveillance data, sufficient information on the sampling strategy

should be provided to allow interpretation of results and comparisons with other surveillance programmes that may have different sample collection points.

Figure 1.1 provides an overview of sampling considerations at different points along the food animal production/slaughter/retail continuum. In general, sampling at the production site (e.g. on farms or in aquaculture facilities) will produce bacterial strain types and resistance patterns most directly associated with the antimicrobial use environment, but that may not reflect the strains surviving processing and reaching the food supply. Environmental sampling (e.g. composite chicken litter samples) may be considered as an alternative to individual animal sampling when necessary, as long as representativeness has been established. *Salmonella* serotypes in an animal vary with time and place in the production chain (5, 6, 7). Other factors that may affect results include season, latitude, processing methodology, transportation and storage.

Slaughterhouses are usually the most convenient and affordable point for collection of animal samples. It is generally preferable to collect caecal samples, although this option may be limited by practical difficulties or cost. Caecal samples generally provide a higher recovery of isolates than carcass or rectal swabs, and better reflect farm-level exposure in individual animals (by reducing the likelihood of contamination from the processing environment). It should be noted that the microbiota of the animal caecum may be affected by the time spent in transport and in holding pens, and the persisting microorganisms that can be acquired in each environment.

1.7.2 Sample information

It is important to record basic information on each sample. This will allow more comprehensive analysis of laboratory data, help clarify potential biases for different sample types, and help identify critical control points for mitigating resistance.

- For isolates from *humans*, basic information includes age (or date of birth), sex, specimen type, geographical location and hospitalization status. Other useful information that could be obtained from sentinel sites or during special studies may include recent travel history, previous and current antimicrobial use, immune status, whether the sample was collected as part of an outbreak investigation and, if so, any data from the investigation, including the known or suspected food source.
- For isolates from *retail foods*, useful information includes store location, processing plant, origin (imported or domestic), whether fresh or frozen, organic or conventional production, and if the food was prepackaged or subject to in-store processing. Much information can be captured simply by filing a copy of the package label.

- For *food animal* samples collected during production, information may include animal species, time and place of collection, age and clinical status of the animal, and possibly the history of antimicrobial use on the farm. For samples collected at slaughter, information may include the origin of the animal (domestic or imported), slaughter class (e.g. dairy or beef cattle), and the processing plant.

1.7.3 Sampling approaches

Sampling may be active (prospective) or passive (samples collected for other purposes), random or systematic, statistically based or convenience. Sentinel surveillance, which relies on specific providers, hospitals, laboratories, or other sources reporting a disease or condition under surveillance, may also be employed. For antimicrobial resistance surveillance, this would include providing antimicrobial susceptibility results or submitting specimens or isolates for testing. Sentinel surveillance requires fewer resources and is often more complete and timely than population-based surveillance, but it may not be representative of the entire population. The relative strengths and limitations of the different approaches should be considered when establishing a surveillance programme and when interpreting and comparing results.

1.7.4 Sampling frequency

In order to permit analysis of trends in antimicrobial resistance, sampling should be done on a continuous or regular basis using consistent methods. The frequency of testing should be decided on the basis of the incidence and seasonality of the bacteria or diseases under surveillance. In many established surveillance systems, samples are collected monthly. If resources are not adequate for such frequent testing, isolates should be collected periodically throughout the year from different sites in sufficient numbers to identify trends.

1.7.5 Sample size

Several statistical methods can be used to calculate the number of isolates needed for testing (sample size). Sample size will depend on the desired precision for estimates of the prevalence of resistance and the magnitude of change in resistance to be detected over a specified period of time. Sample size also depends on the initial or expected prevalence of resistance and the size of the population to be monitored, as well as the desired level of statistical significance and power to detect a difference. There are a number of statistical software packages and sample size calculators that can be used to calculate sample size. In addition, the European Food Safety Authority has compiled tables showing required sample sizes for different antimicrobial resistance monitoring programme objectives (8).

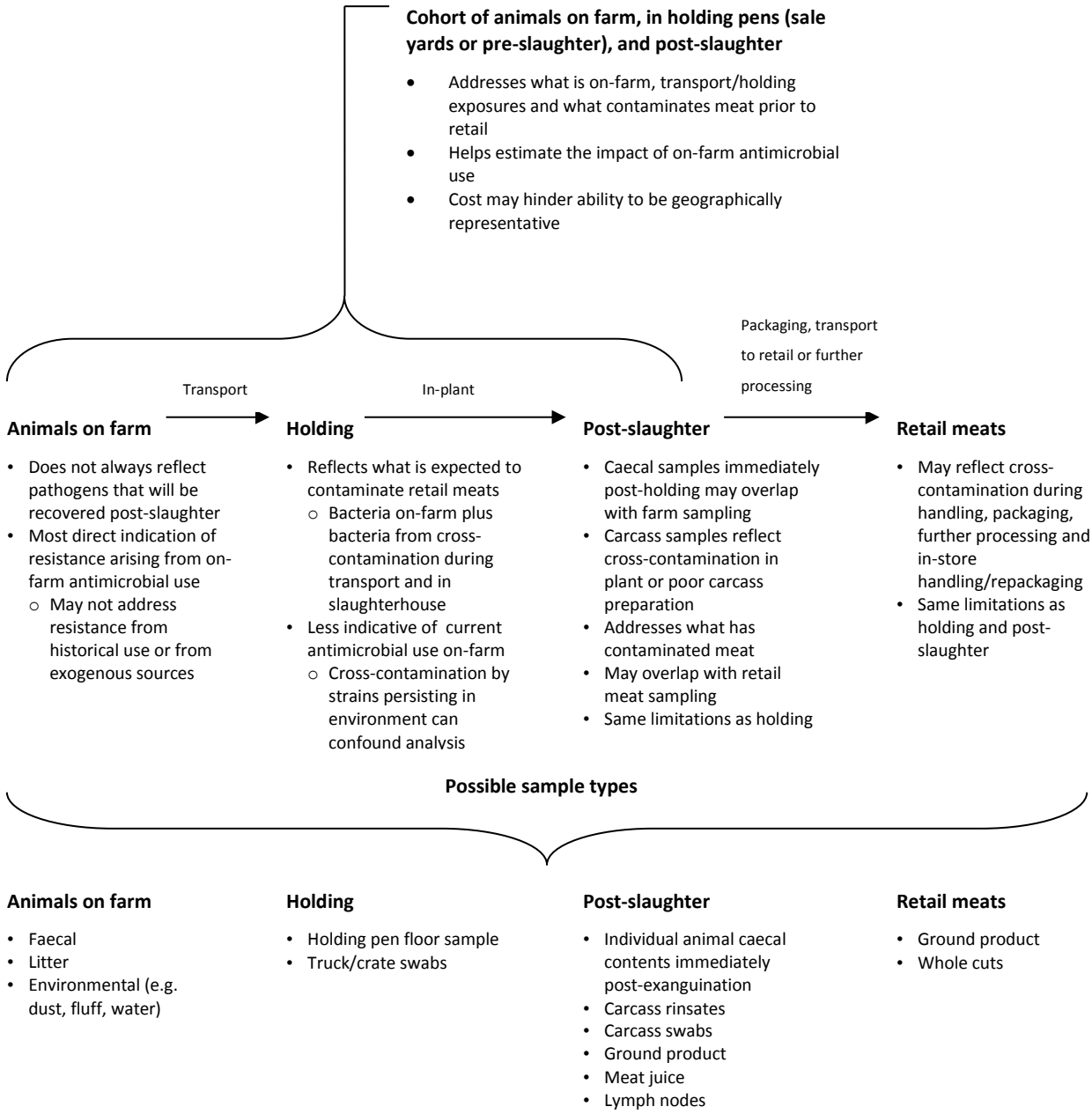

Figure 1.1. Examples of sampling considerations through the production/post-harvest continuum

1.8 Laboratory testing

A sound surveillance programme should include access to a laboratory that is able to do at least the following.

- Isolate, on artificial growth medium, the target pathogens from different specimen types.
- Identify bacteria to the genus and species levels using accepted microbiological methods.
- Determine serotypes of *Salmonella* or have access to a reference testing centre.
- Perform antimicrobial susceptibility testing using validated methods according to established standards, such as those of the Clinical and Laboratory Standards Institute (CLSI) or the International Organization for Standardization (ISO).

WHO capacity-building activities, such as the Global Foodborne Infections Network (GFN), may be able to provide technical support and training in food microbiology to help implement testing. In addition, participation in an external quality assurance programmes, such as GFN's External Quality Assurance System (EQAS), is recommended.

1.8.1 Bacterial culture methods

Different recovery methods can differentially enrich for bacterial subpopulations within a sample. Culture methods and media should meet recognized international laboratory standards. As with other design considerations, culture methods should be defined beforehand and be described in surveillance reports. Differences in culture methodology should be taken into account when data from different surveillance programmes are compared.

1.8.2 Storage of bacterial isolates

Monitoring laboratories are encouraged to collaborate with established monitoring systems, national reference laboratories, WHO collaborating centres and other partners to provide long-term storage for a representative number of isolates that can be used for future testing and analysis.

1.8.3 Isolate identification

Bacteria should be identified to the species level. For *Salmonella*, serotype information is fundamental to understanding the epidemiology, including of drug-resistant strains. However, not all laboratories would necessarily test for all possible serotypes of *Salmonella*. The most common serotypes in a given area should be known in order to ensure an adequate supply of antisera.

1.8.4 Standardized antimicrobial susceptibility testing and quality control

Only in vitro antimicrobial susceptibility testing methods that have been standardized and validated under the auspices of an internationally recognized consensus standards organization, such as CLSI or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), should be used. This is a critical feature of a sound antimicrobial resistance surveillance system, and is the only way to ensure reliable data. The steps in these official standards should be strictly followed and should not be modified for local use.

EUCAST and CLSI standards cover test performance and interpretation for both disc diffusion and minimum inhibitory concentration (MIC) methodologies. In either case, quantitative results (disc diffusion zone diameters or MIC values) should be measured and recorded, in addition to the categorization of an isolate as susceptible or resistant. Tracking changes in the distribution of quantitative results can be very helpful in following bacterial resistance patterns over time, and also allows retrospective data analysis if breakpoints or cut-off values are changed.

Susceptibility testing methods for *Salmonella* and *E. coli* are well known and widely available. Validated testing methods for *Campylobacter* were developed more recently and are less widely known. CLSI has established the quality of a disc diffusion method for screening isolates for resistance to erythromycin (15 µg disc) and ciprofloxacin (5 µg), where growth up to the disc (i.e. no zone of inhibition) indicates acquired resistance determinants in *Campylobacter* that correlate with tentative resistance breakpoints (9). A EUCAST disc-based method has been used to establish epidemiological cut-off values (ECOFFs) using the same erythromycin and ciprofloxacin disc masses, as well as tetracycline (30 µg). This method uses a different test medium and incubation conditions (10), but the same quality control organism (*C. jejuni* ATCC33560). No other method of disc diffusion testing has been formally validated for *Campylobacter*, although comparison studies have been conducted.

For *Campylobacter* testing by broth microdilution, a standardized method is available for testing azithromycin, chloramphenicol, clarithromycin, ciprofloxacin, clindamycin, doxycycline, erythromycin, gentamicin, florfenicol, levofloxacin, meropenem, nalidixic acid, telithromycin and tetracycline (9, 11, 12).

Quality control

Quality control (QC) testing and frequency should follow international guidelines. Expert rules for discordant susceptibility results, as published by CLSI and EUCAST, should be applied to ensure data

integrity. The presence of contaminants, incorrect identification of bacteria, user error and the use of non-validated methods are the most common reasons for inaccurate susceptibility testing results.

Recommended antimicrobials for surveillance of *Salmonella* and *E. coli*

Some antimicrobial agents are clinically useful, while others are epidemiologically useful. It is therefore proposed that the following antimicrobials should be used for testing *Salmonella* and *E. coli:*

- ceftriaxone (recommended) or cefotaxime,
- nalidixic acid (optional),
- ciprofloxacin,
- ampicillin,
- tetracycline,
- chloramphenicol,
- gentamicin,
- trimethoprim-sulfamethoxazole.

Streptomycin resistance is useful for tracking certain strains of *Salmonella* (e.g. *Salmonella* serotype typhimurium DT104) but results are often unreliable. Trimethoprim and sulfamethoxazole are tested separately by some programmes for epidemiological purposes.

Recommended antimicrobials for surveillance of *Campylobacter*

As a minimum, *Campylobacter* should be tested for resistance to erythromycin and ciprofloxacin. Testing parameters have been established for other agents that may be medically useful (see above).

Other bacteria

For other bacteria, the selection of antimicrobials for testing will depend on the particular organism. *Enterococcus* is often used to monitor resistance to antimicrobial agents with Gram-positive activity. Information on antimicrobial compounds for monitoring susceptibility in *Enterococcus* can be found on the Websites of the surveillance programmes listed in Annex 2.

1.9 Data analysis and reporting

Reporting in an integrated manner should include comprehensive analyses of surveillance data from all sources. This requires joint evaluation of the data, with the involvement of microbiologists,

epidemiologists, clinical practitioners and food scientists. Depending on the size of the project or programme, it can be advantageous to appoint a coordinating body to audit and evaluate the surveillance findings. The coordinating body should organize and direct the analysis to help ensure that the integrated analysis, reporting and risk communication are done properly and in a timely manner. This group can also ensure that the programme continues to meet the intended public health needs, as outlined in the programme scope, and recommend modifications to address emerging issues.

It is important that the data are analysed with an emphasis on the human health significance of the findings. Surveillance results should be transparent and easily accessible, and should be communicated in language that can be understood by non-specialists. It is helpful to compose narrative summaries, written in plain language, to accompany the data, to help consumers understand the risks and hazards and the meaning of significant trends.

1.9.1 Programme description

To provide context for the surveillance findings, the programme structure and methodology should be described in sufficient detail to permit others to make sound comparisons with other programmes and their results. This should include: a description of the sampling design and specimen collection; the microbiological methods used for culture, identification and susceptibility testing; the interpretative criteria used for reporting; quality control and quality assurance measures; a glossary of terms; statistical methods; and any changes made in the methodology over time.

1.9.2 Interpretation of data

To ensure harmonized reporting of surveillance data and facilitate comparison of results, it is recommended that epidemiological cut-off values be used when interpreting the results of in vitro antimicrobial susceptibility tests (13).

Epidemiological cut-off values are the MICs that distinguish strains with an acquired decrease in susceptibility (non-wild-type populations) from wild-type susceptible populations. Classifying strains relative to wild-type susceptible populations provides a relatively stable and discrete reference point for tracking changes in susceptibility over time. This approach also permits direct comparison of data from different surveillance systems with different clinical breakpoints. Because ECOFFs are empirically determined from a representative distribution of MIC values in the target population, this approach also largely avoids the need to reanalyse historical data when clinical breakpoints change (as often occurs when new clinical data are collected). The use of ECOFFs is also beneficial

when no breakpoints have been formally established from clinical outcome data, such as for *Campylobacter*. For a thorough treatment of this issue, see reference 14.

It is important to note that the use of epidemiological cut-off values has led to confusion over the definition of resistance. This has traditionally been defined clinically as a means of predicting the likelihood of success of antimicrobial therapy. Historically, the resistant category has been established using extensive data sets that combine pharmacological parameters and clinical outcome studies with MIC data from wild-type populations. For this reason, it has been recommended that the term resistant be reserved for cases where clinical breakpoints have been formally established following clinical trials (14). As a minimum, in reporting, the way in which the term is used should be clarified to avoid misunderstanding.

1.9.3 Data presentation

To promote the comparability of data from different systems, quantitative data should be presented in a format that allows different interpretative criteria to be applied. As noted above, this should take the form of MIC distributions or zone diameters (see section 5 for examples of data presentation).

Databases should be designed in a way that allows data to be extracted appropriately. For ease of analysis and reporting, data should centre on individual isolate identifiers with links to metadata, including denominator data. The database needs to allow data to be shared while maintaining confidentiality. The WHONET data management software does this and is available free of charge (http://www.whonet.org). The software can be customized for local monitoring purposes and meets most data management needs. WHONET was developed and is maintained by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance at the Brigham and Women's Hospital in Boston, USA. Section 5 contains a detailed description of data management.

Where possible, surveillance data should be analysed in conjunction with other available data sets, such as information on antimicrobial use, pulsed-field gel electrophoresis (PFGE), whole genome sequences, plasmid typing data (or other strain typing data), as well as outbreak investigations involving isolates recovered in surveillance. More information on the design of antimicrobial resistance surveillance programmes and analysis of data is given elsewhere (15).

Once data integrity and confidentiality have been ensured, data should be made freely available for independent analysis and reporting.

1.10 Refining the monitoring system

In building an integrated monitoring system, resources generally go initially to designing, coordinating and implementing the system, designing valid sampling and culture methods, establishing partnerships to acquire samples, securing reagents for culture and instruments to conduct routine testing, validating and analysing the data, and developing expertise through training. Once these fundamental components are in place, other goals of integrated surveillance can be considered. These include the following.

1. Increase the timeliness of data collection and reporting. Data collection should occur at least annually, although not necessarily for all target organisms and all study populations.
2. Establish avenues of cooperation, communication and data publication between agencies and disciplines.
3. Publish analyses describing emerging and ongoing human public health issues related to resistant pathogens.
4. Carry out research to support and develop surveillance, identify intervention points, and track the spread of resistance genes between ecological niches.
5. Collect and report subtyping data (e.g. PFGE, phage type, genomic sequence) for serotypes with important resistance patterns.
6. When possible, compare monitoring data with data on strains isolated from clinical veterinary cases, to evaluate the utility of clinical isolates as an early warning system.
7. Periodically evaluate the surveillance methods used and the data collected to ensure that they are the most useful for public health purposes; make adjustments to address emerging hazards, e.g. other pathogens and commodities.
8. Improve methods, but ensure that improvements do not compromise comparisons with historical data.
9. Collaborate with colleagues in other countries to ensure that new methods are adopted in a way that enables and encourages comparison of data among countries.
10. Report data on resistance together with data on antimicrobial use in humans and animals, to help increase understanding of practices that may contribute to resistance.

Surveillance systems in several countries can be used as models for new national programmes. These include, but are not limited to, the Danish Integrated Monitoring Programme (DANMAP), the US National Antimicrobial Resistance Monitoring System (NARMS), the Canadian Integrated Programme for Antimicrobial Resistance Surveillance (CIPARS), the National Antimicrobial Resistance Monitoring

Programme (NAMP) in the Republic of Korea, Norway's NORM-VET programme, and the Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) programme. These and other programmes were listed in the report of the first meeting of AGISAR (16).

1.11 References

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Surveillance of the consumption of antimicrobial agents in humans and animals

2.1 Background

Surveillance of the consumption (usage and overall sales) of antimicrobial agents in humans and food-producing animals is important, as it allows integrated analysis together with data obtained from surveillance of antimicrobial resistance. At the international level, several organizations have recognized the importance of such analysis and have documented its objectives. For example, in 2000 a WHO consultation drafted a set of global principles for the containment of antimicrobial resistance in animals intended for food (1), which included the following recommendations:

> "Relevant authorities should establish systems to determine the amounts of antimicrobials given to food animals."
>
> "Information on the amounts of antimicrobials given to food animals should be made publicly available at regular intervals, be compared to data from surveillance programmes on antimicrobial resistance, and be structured to permit further epidemiological analysis."

In 2001, another WHO consultation (2) concluded that monitoring of antimicrobial usage in food animals is needed for:

- policies for the containment of antimicrobial resistance;
- comparison of the use of antimicrobials at different levels (local, regional, national, international);
- information and education of stakeholders;
- correlation with data from antimicrobial resistance monitoring in humans, animals, and food;
- application of risk analysis processes pertaining to the issue of antimicrobial resistance; and
- evaluation of the impact of implementation of the prudent use of antimicrobials and of other interventions.

Updated standards are available on monitoring the consumption of antimicrobial agents used in food-producing animals (3) and in aquatic animals (4).

WHO has been active for many years in various aspects of the surveillance of drug consumption in humans (5-7). Surveillance data may be either quantitative or qualitative. Quantitative data are useful in describing quantities and frequency of use of antimicrobial agents in various parts of the health care system, in order to identify trends over time or to make comparisons between facilities, countries or regions. Such data may be collected from wholesalers, pharmaceutical companies or pharmacies, or through regular surveys. Qualitative data can describe the reasons for use of antimicrobial agents, and may be collected from inpatient or outpatient records (5).

In Europe, notable advances have been made at both the country and regional level. Surveillance of antimicrobial consumption in humans is coordinated by the European Centre for Disease Prevention and Control (ECDC), through the European Surveillance of Antimicrobial Consumption Network (ESAC-Net). This is a network of national surveillance systems that provides European reference data on antimicrobial consumption in the community and in hospitals.

The surveillance of antimicrobial consumption in animals is more complex than in humans because of variations in usage patterns in different animal species and production types (e.g. beef and dairy cattle). Surveillance of consumption of antimicrobial agents in animals is coordinated by the European Medicines Agency (EMA), through European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Currently, ESVAC collects information on overall national sales of veterinary antimicrobial agents across the European Union (EU). Some other countries, such as Canada and the United States of America, also collect overall sales data on veterinary antimicrobial agents and antimicrobial growth promoters.

2.2 Terms of reference

This section, together with sections 3 and 4, aims to support and promote the collection of standardized data on the usage of antimicrobial agents in humans and animals, including farmed fish, at local and national levels. Section 3 provides guidance and tools for collection of data on usage of antimicrobial agents in humans, while section 4 provides guidance on the collection of point prevalence data on consumption of antimicrobials in animals at the farm level.

2.3 General considerations

It is generally acknowledged that approaches to collecting data on consumption of antimicrobial agents will vary from country to country, because of variations in the infrastructure of drug distribution systems. However, the following basic main steps should be included in all surveillance systems (8).

1. Describe the system of distribution of antimicrobial agents in the country and identify sales points outside the mainstream regulatory system, e.g. Internet sales, import of medicated animal feeds and movement of antimicrobial agents across borders.
2. Identify the antimicrobial agents in commercial circulation.
3. Identify potential points of data collection.
4. Assess what each data source represents.
5. Set parameters for precision and completeness of the surveillance system.
6. Establish priorities according to the needs and resources available.
7. Consider and address the need for confidentiality and data protection.

National-level data on overall sales of antimicrobial agents for human and veterinary medicine are useful for documentation of trends in consumption, interpretation of resistance patterns at national level, risk assessment, and other purposes. Sections 3 and 4 describe the purposes of surveillance of human and non-human antimicrobial consumption and identify potential sources of data, and classes and types of antimicrobial agents to include in the surveillance programme. They emphasize the need for standardized data collection and reporting, including use of the Anatomical Therapeutic Chemical (ATC) classification systems. Variables that should be collected for each antimicrobial product (veterinary or human) are described.

Data on consumption of antimicrobial agents can also be collected from end-users, such as physicians, veterinarians and farmers, through point prevalence surveys and longitudinally. The data sources could be, for example, treatment diaries, bills or electronic records. Local consumption data,

e.g. at herd, hospital or community level, are usually needed to understand and interpret local AMR data. In addition, if nationally representative samples are used, such as surveys of representative hospitals, veterinary clinics or farms, point prevalence and longitudinal approaches may provide an alternative means of collecting national-level consumption data, particularly for countries that cannot collect these data directly from wholesalers, pharmacies or pharmaceutical companies. In the case of veterinary medicine, national overall consumption data are not species-specific, since most antimicrobial medicinal products are approved for several species. Point prevalence and longitudinal approaches can therefore be helpful in estimating consumption at the species level, both locally and nationally.

At the national level, overall usage data should be reported on a regular basis. Reporting should be standardized, and the appropriate denominator should be specified. If the relationship between use and resistance is to be analysed, it is important that both datasets are appropriate for this purpose. Similarly, caution should be exercised when interpreting temporal associations between consumption and antimicrobial resistance data that may be observed in data obtained through longitudinal studies.

2.4 Collection and reporting of data on consumption of antimicrobial agents in humans

2.4.1 Surveillance of consumption of antimicrobial agents in hospital settings

Given the usually high level of consumption of antimicrobial agents in hospitals, and the impact of antimicrobial resistance on morbidity, mortality and the cost of health care, it is recommended that surveillance of consumption of antimicrobial agents in these settings be given priority. In addition to quantitative information on the consumption of different antimicrobial agents, qualitative information can be obtained on indications for antimicrobial use, linkage with resistance data, and the identification of areas for quality improvement.

Point-prevalence surveys, particularly if repeated over time, are a simple and inexpensive way of identifying prescribing trends, linking results with antimicrobial resistance data, and identifying areas for improvement. Although cross-sectional surveys cannot quantify the exact amount of antimicrobials used in a given hospital, a reasonable estimate can be obtained, based on the number of hospital admissions and the ages and diagnoses of the patients. Longitudinal studies and continuous surveillance programmes, albeit more labour-intensive, allow prospective audits of consumption of antimicrobial agents with direct interaction and feedback to prescribers, a strategy

that has proven effective for improving antimicrobial prescription and reducing costs. Data on prescriptions of antimicrobial agents can usually be provided by the hospital pharmacy department.

2.4.2 Surveillance of consumption of antimicrobial agents in the community

There is growing evidence of an association between use of antimicrobial agents and antibiotic resistance in pathogenic organisms at the community level. Surveillance of the outpatient consumption of antimicrobial agents can provide a benchmark for comparison of antimicrobial consumption between areas and countries, and identify the need for specific interventions. Measuring consumption of antimicrobial agents is usually more complex in the community than in hospitals. National sales data are not available for most countries. Alternative strategies include: (1) use of data on bulk purchases provided by retail pharmacies; (2) exit interviews at pharmacies or sentinel primary care clinics; and (3) prospective household surveys.

2.4.3 Reporting of consumption of antimicrobial agents in humans

Antimicrobial consumption data need to be reported in a way that allows comparison between different areas and countries. Ideally, the same classification system and indicators of use should be used. Standard indicators of hospital antibiotic consumption are the daily defined dose (DDD) and days on therapy (DOT) per 100 bed-days. The most widely used indicator for outpatient antibiotic consumption is DDD per 1000 inhabitant-days.

2.5 Collection of data on antimicrobial usage in animals

Guidance on surveillance of overall sales of antimicrobial agents used in animals has been published previously (9). ESVAC has developed a veterinary antimicrobial consumption data collection form for overall sales of antimicrobial agents at the national level, as well as an example to show how the form should be completed (10). OIE international standards provide further information (3, 4).

Section 4 provides guidance for collection of point prevalence data on consumption of antimicrobial agents in animals at farm level, including selection of animal species for data collection, recruitment and sampling of farmers, type of data to obtain, and basic approaches to data collection. Additional information on collecting species-level data and on technical units of measurement for reporting these data is currently under development by ESVAC (11).

Information on consumption by animal species, production type and age class is needed to allow analysis with more refined units of measurement, such as defined daily dose animals (DDDA) or defined course dose animal (DCDA). Such information is also necessary to assess and follow prudent use practices. Based on information in the marketing authorization, formulation and strength, data

on overall sales can be split into products intended for companion animals and those generally used for food-producing animals and horses. However, as products are often authorized for multiple animal species, other data collection systems are needed to get a further stratification to animal species, production types and age groups. Automatic data collection systems, in which all information on use of antimicrobial agents is entered in a database, can provide very precise information (12) but require infrastructure and resources for continuous management of the system. In some countries, the marketing authorization holders are able to provide estimates of sales per animal species. The accuracy of information gathered by such systems must be assessed; if the precision is acceptable, such systems are an option that is less demanding of resources. For an example of this approach, see Chevance & Moulin (13). Finally, data collected in point prevalence or longitudinal studies can be used to stratify overall sales data by extrapolation.

2.5.1 Reporting of consumption of antimicrobial agents in animals

Overall national sales data should reflect the total quantity of antimicrobial agent (e.g. mg of active substance) sold per unit of time (usually one year). This should be expressed relative to an appropriate denominator representing the animal population at risk (e.g. kg for slaughtered pigs, poultry, cattle, etc. or numbers of live animals) for the corresponding year. In Europe, the denominator used by ESVAC is the population correction unit (PCU), which is an estimate of the combined weight of livestock and slaughtered animals in the country. The PCU takes into account the animal weight at the time that treatment was most likely given, and that animals transported for slaughter or fattening in another country are likely to have been treated in the country of origin (14). Overall sales data of given antimicrobial agents in Europe are expressed as mg/PCU, where 1 PCU = 1 kg of different categories of livestock and slaughtered animals (14).

Species-level data should be reported in a standardized fashion that takes into account the numbers of animals treated over the reporting period. While at the international level, defined daily doses for humans have been assigned to antimicrobial agents for use in standardized reporting (15), an equivalent measure for animals has not been agreed internationally. Some countries have adopted the animal defined daily dose animals (DDDA) (16). Reporting may also include the duration of treatment. Further information is available elsewhere (16).

2.6 References

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Collection of data on usage of antimicrobial agents in humans

A variety of approaches are available for measuring consumption of antimicrobial agents, varying in purpose, setting, methodology and output. This section gives guidance on three important approaches: collection of point prevalence data on antimicrobial use in hospitals; collection of longitudinal data on antimicrobial use in hospitals and the community; and collection of information on the volume of antimicrobials consumed through the use of continuous surveillance programmes.

3.1 General considerations

3.1.1 Confidentiality

It is important to ensure that information on individual patients is kept confidential. In many countries, privacy laws require individual patient consent or the approval of an ethics committee before this type of information is collected. In any case, all patient data must be anonymous. Participants also need to be assured that individual hospital names will not be revealed in any internal or external report.

3.1.2 Antimicrobials under surveillance

Antimicrobials that may be considered for surveillance are listed in Table 3.1. As a minimum, information on use of antibacterials for systemic use (J01) should be collected.

Table 3.1 Groups of antimicrobial agents to be included in the surveillance

Groups of antimicrobial agents	ATC codes
Antimicrobial agents for intestinal use	A07AA; A07AB
Antimicrobial agents for systemic use	J
Antibacterials for systemic use	J01
Antimycotics for systemic use	J02
Antimycobacterials	J04
Antivirals for systemic use	J05

Groups of antimicrobial agents	ATC codes
Antimicrobial agents used as antiparasitic agents	P01AB
Antimalarials	P01B

3.2 Collection of point prevalence data on antimicrobial use in hospitals

Point prevalence surveys[1] (PPS) can give useful data on patterns of hospital antimicrobial prescribing, providing insight into the determinants of antimicrobial use. Data obtained from PPS can be used to:

- compare antimicrobial use in different countries or regions (quantitative and qualitative);
- identify targets for quality improvement (e.g. adherence to hospital guidelines, documentation of antibiotic therapy, peri-operative prophylaxis);
- help design hospital interventions aimed at promoting appropriate use of antimicrobials; and
- assess effectiveness of interventions (if repeated regularly, e.g. quarterly).

Nationally, PPS data for hospitals should be collected annually, preferably supported by a national surveillance network. Ideally, prevalence data in hospitals should be collected routinely (for example 4 times a year) as part of an ongoing monitoring programme. Public policies and specific interventions to improve the quality of antibiotic use should be informed by the surveillance data. The first step in improving the quality of antibiotic use is to establish the extent of inappropriate use of antibiotics.

Meaningful comparisons of antibiotic use patterns can only be made between studies using similar study designs, definitions and data collection methods. The cross-sectional PPS design is useful in this regard because it is relatively simple to implement and can be structured to collect basic information on patients (antibiotic treatment, indication for treatment, the underlying disease).

3.2.1 Type and quality of end-user data collection

For point prevalence surveys, data can be extracted from various sources, preferably written sources, such as patient records and computer databases.

[1] A point prevalence survey or study is a cross-sectional study, which provides a snapshot of drug use at a particular point in time.

It is strongly recommended that pilot studies of patient-level data collection should be conducted before the full point prevalence survey. The pilot study will help evaluate and refine the methodology, for example, by identifying problems in the survey design and data analysis and providing an estimate of the workload in time per patient.

Ideally, participating physicians should be asked to conduct a one-day cross-sectional hospital-based PPS, in which all included hospital wards are audited once. The types of ward to be included should be predefined. The surveys should not take place at the weekend or on public holidays. Surgical wards should not be audited on the day after a weekend or public holiday, in order to capture information about prophylaxis in the previous 24 hours. Medical wards may be audited on any weekday.

In some countries, it may not be feasible to survey an entire hospital in one day. In this case, the survey can be conducted over several days, with a maximum of two weeks. In order to avoid duplicate records resulting from movement of patients within the hospital, it is recommended that a whole ward should be surveyed on one day.

3.2.2 Recruitment

When organizing a PPS on a provincial or national level, a wide variety of hospitals with different ward and patient characteristics should be recruited to ensure that data are representative. In principle, efforts should be made to ensure that the sample of participating hospitals is representative of the larger (e.g. national) population. The sample should be random, possibly stratified by hospital type or size. Any interested hospital-based physician should be able to indicate his or her interest in the PPS, for example by contacting a study coordinator. Participating physicians could be invited through national or local associations and conferences.

A PPS is best carried out by a multidisciplinary team of health professionals, including, where available, infectious disease specialists, infection control teams, clinical microbiologists, epidemiologists and clinical pharmacists. Members of the team should receive a detailed standardized protocol to ensure uniformity of data collection.

3.2.3 Inclusion and exclusion criteria

The following is an example of inclusion criteria from studies in Europe (1-4):

> Detailed data are recorded “only for inpatients with active antimicrobial prescriptions” at 08h00 on the day of survey. Prescriptions newly prescribed after 08h00 on the day of the

survey are excluded. An inpatient is a patient who stayed in hospital overnight, i.e. was admitted to the ward before 0h00 on the day of the PPS.

Day care patients and outpatients are defined as ambulatory care patients, and are excluded. Emergency admissions on the day of the survey are also excluded.

3.2.4 Denominator data

The following are examples of definition of the denominator from studies in Europe:

- Total number of eligible inpatients at 08h00 on the ward surveyed. Data from patients discharged before 08h00 and patients admitted later are not collected.
- Total number of eligible beds attributed to inpatients at 08h00 on the ward surveyed (occupied and empty beds).

Participants need to provide information on the actual situation on the day of the PPS.

3.2.5 Data collection

Antimicrobials that could be included in the surveillance are listed in Table 3.1.

The following data should be collected: the patient's age, sex, weight and ventilation status; the antimicrobial agent, single unit dose and number of prescribed doses per 24 hours; route of administration; anatomical site of infection; whether infection was acquired in the community or in hospital; details of prophylaxis for surgical patients (duration of prophylaxis 1 dose, 1 day, or >1 day); and whether or not a diagnosis or indication for treatment was recorded in the notes when antimicrobial treatment was started. To facilitate data collection on reason for treatment, a predefined list of grouped items may be used. Co-morbidities may also be recorded. If all patients (including those not receiving antimicrobial treatment) are surveyed, the age, sex and possibly co-morbidities should be recorded. As a minimum, all patients receiving antibacterial drugs (J01) should be surveyed, with information on indication for use, dose and the patient's age and sex.

After the survey, the prescribed antimicrobial products should be grouped according to the ATC classification (5). This will allow standardized reporting and comparison of results.

Data should be collected on two types of paper form: one for department (denominator) data and one for individual patients. A Web-based application, designed by the Laboratory of Medical Microbiology of the University of Antwerp, Belgium, may be used for data entry and reporting (http://app.esac.ua.ac.be/arpec_webpps/). This application requires a defined stepwise manner of data entry. Each participating hospital needs to be registered, with the name, geographical location and type of hospital (primary, secondary, tertiary or specialized, and teaching or non-teaching). The

software includes several online checks to help prevent mistakes in entering the data. An online validation procedure can signal errors in the survey or provide warnings of possible discrepancies. Supplementary data cleaning (e.g. detection of unexpected doses) leads to direct contact with the participant concerned to verify and, if needed, modify the data online. Hospitals can extract their data at any time for verification or analysis. After online validation, a standardized feedback report can be downloaded.

3.2.6 Data reporting

The principal indicators produced by this type of survey will be prevalence rates for individual antibiotics, expressed as number of treatments per 100 patients. If information about daily doses is collected, average prescribed doses can be computed. Other descriptive statistics, such as overall prevalence of antimicrobial use, and use by ward, infection site and antimicrobial class, can also be reported.

3.2.7 Strengths and limitations of the PPS method

The uniformity of data collection and the data validation process described here help guarantee a standardized, solid database for cross-sectional analyses and further longitudinal studies. A PPS study allows determinants of antibiotic use among inpatients to be investigated. The simplicity of the protocol makes the survey feasible, achievable and sustainable. It offers simple case definitions to aid auditing of antibiotic use, without recourse to complicated algorithms, such as diagnostic criteria. It further collects detailed data only on patients with an active antimicrobial prescription, and not on all inpatients. This study design can simply measure drug use, or can be used for a criterion-based assessment of drug use in relation to guidelines or restrictions. If repeated regularly, such studies can contribute to sustained awareness of the need for careful use of antibiotics, and can be used to evaluate hospital-based interventions, such as the development of a local antimicrobial stewardship programme. The online data-entry and reporting tool offers the opportunity to include other data; for example, participants may be invited and encouraged to complete other questionnaires, e.g. on their current empiric antibiotic guidelines.

The generalizability of the findings could be limited by the methodological approach. A one-day PPS in a small hospital, for example, would capture small numbers of patients with specific conditions. The PPS should therefore not be used for benchmarking. Nevertheless, antimicrobial use prevalence rates obtained through repeated PPS seem to remain stable over time (1). The PPS does not collect information about the clinical justification and duration of antibiotic therapy, whether a suitable culture was obtained, whether the treatment is appropriate for the infection, or whether the

surgical prophylaxis and its duration are justified. Other study designs, e.g. longitudinal studies, would be needed to collect such information.

3.3 Longitudinal surveys of antimicrobial use in hospitals and the community

Longitudinal studies[1] may provide much more detailed information on antimicrobial use then is possible with point prevalence studies. For example, longitudinal methods allow both incidence and prevalence to be estimated, and longitudinal follow-up gives information about treatment duration and patient risk factors. Although such studies are time-consuming, they are often worth while because they give a clearer picture of what is happening at the patient level.

Longitudinal studies can be performed both in health institutions and in the community setting. They are easier to perform in health institutions (e.g. hospitals and nursing homes) where conditions can be more easily controlled than in the community. The studies may be prospective or retrospective (of prescription databases or medical records). In addition to information about patients, indications and antimicrobial agents, longitudinal studies can provide information about disease outcome, clinical presentation, laboratory results (e.g. C-reactive protein (CRP), leukocytes, microbiological tests) and duration of treatment. As electronic prescribing becomes more common, databases are being developed to provide full medical and prescribing information on a continuous basis at the individual level. Such databases are very powerful, and can address a range of issues, including reasons for changes in therapy, adverse effects and health outcomes.

Ideally, data should be collected routinely as part of an ongoing monitoring programme. Data may be collected continuously, over a defined period (i.e. as part of daily work), or on a rotating basis, e.g. by time, disease, prophylaxis procedures, ward or type of patient. Nationally representative data should be collected annually, if possible.

It is important that the sample chosen is as valid and representative as possible. Epidemiological and statistical expertise is therefore desirable when designing the survey. Nevertheless, collecting accurate data may be a challenge, and it is important to focus on the most essential information; data collection may have to be limited in order to obtain maximum compliance.

[1] A longitudinal study involves collection of information on antimicrobial use and other relevant patient and denominator data over a specified period of time, normally of sufficient duration to allow reliable estimation of treatment incidence and other parameters.

3.3.1 Type and quality of data collection

Collection of end-user data can be challenging and there are a number of barriers to the acquisition of high quality, comprehensive data on antimicrobial use. Ideally, accurate, detailed data should be obtained from all persons using antimicrobials. Only a few countries have mandatory and automated reporting systems using sales data from pharmacies or prescription data from prescribers. In this setting, it should be remembered that information on sales and prescriptions does not necessarily reflect exact usage, since patient adherence is a confounding factor. Most countries do not have good registries or other sources of information on antimicrobial use, and periodic surveys are often needed.

3.3.2 Recruitment

It is rarely possible, for logistic reasons or because of resource limitations, to include all eligible persons, institutions and general practitioners in a region or country. Therefore some type of sampling is required. Efforts should be made to ensure that the sample of participants is representative of the larger population. As longitudinal studies are time-consuming, efforts should be made to motivate the participants continuously throughout the project, and to encourage them to comply with data collection throughout the study period. If the study is performed in institutions, only a few individuals should be responsible for data collection.

3.3.3 Inclusion criteria

The examples of subject inclusion and exclusion given for point prevalence studies in hospitals (section 3.2.3) also apply to longitudinal studies. In addition, it is necessary to specify the setting (e.g. hospital, community) and period over which data will be collected.

3.3.4 Denominator data

Similarly, the denominator data in longitudinal studies are similar to those for point prevalence studies. In addition, it is necessary to determine how many people were at risk of antimicrobial prescription over the entire course of the study period.

3.3.5 Data collection

It is often not feasible to include all antimicrobials and all types of infection in the monitoring, and a selection will therefore have to be made. Criteria for prioritization could include severity or frequency of particular infections, importance of specific drugs for antimicrobial resistance, or general importance of certain antibacterials (e.g. quinolones, third- and fourth-generation cephalosporins and macrolides). Such a selection allows data to be collected, for example, on

antimicrobial use by type of infection or for the antibiotics that contribute most to the development of resistant bacteria.

A detailed project protocol should always be developed, including the list of variables to be collected. A pilot study is recommended, and data collectors should be trained to ensure that the same procedure is followed.

The data to be collected are similar to those collected in point prevalence studies. However, longitudinal studies provide an opportunity to follow patients through their infection and the course of antibiotic therapy. As a minimum, data should be collected on the products used, the route of administration, the number of persons treated and total number of persons at risk of exposure (located in the area at the time of study) during the period of the study. The duration of the study will depend on the resources available but should be long enough to provide sufficient data, e.g. three months for longitudinal cohort studies. Groups of antimicrobial agents that could be included in the survey, and their associated ATC codes, are shown in Table 3.1. Further information could include dose, duration of treatment, age and sex of the patient, and the purpose of administration (e.g. for prophylaxis or treatment of specific indication). Risk factors for use (e.g. the use of a catheter, immunomodulating treatment, and co-existing diseases, such as chronic obstructive pulmonary disease and cancer) are also important to an understanding of why and for whom antimicrobials are used.

When deciding what additional information to collect, it is important to keep in mind the time that will be needed for data collection and the participants' ability to comply with correct data collection. Too exhaustive data collection may undermine the quality of data.

Data on the general characteristics of the institution, physician-practice or area in question are also valuable (e.g. general housing or grouping information, types of patients or prescribers and demographic indicators).

3.3.6 Data reporting

The standard indicators of antibiotic consumption in hospital are DDDs and DOT per 100 bed-days. The most widely used indicator for outpatient antibiotic consumption is DDD per 1000 inhabitant-days. Other indicators that may be reported include appropriateness of treatment for the indication, appropriateness of the duration of therapy, etc. Longitudinal studies of long duration may also be able to report temporal trends.

3.3.7 Strengths and limitations of longitudinal studies

Properly conducted longitudinal studies provide much of the same data as PPS, together with detailed information on trends in consumption. They allow prospective audits of consumption of antimicrobial agents, with direct interaction and feedback to prescribers, a strategy that has proven effective in improving antimicrobial prescription practices and reducing costs. They can also investigate the clinical justification for antimicrobial therapy and its duration, and whether or not suitable ancillary tests (e.g. culture and sensitivity) were carried out.

The limitations of longitudinal studies are related to their greater complexity, cost and difficulty compared with PPS.

3.4 Continuous surveillance programmes

While point prevalence surveys and longitudinal studies are valuable approaches for collection of data on antimicrobial use, and particularly for understanding the factors underlying such use by patients at the hospital or community level, they may not be well suited to simply measuring the volume of antimicrobials consumed. A continuous surveillance programme is a simpler approach to collecting such data and can be applied in either a hospital or a community setting. Most continuous surveillance programmes are carried out in health institutions, because of the easy availability of the relevant data and resources needed.

3.4.1 General considerations

A continuous surveillance programme can be defined as a system for making regular measurements of the volume of antimicrobials consumed. Such programmes often have an important computerized component, as the same task is repeated over time. Unlike longitudinal surveys, which collect data at the patient level, continuous surveillance programmes tend to use a single central source of data and are designed to be sustainable.

3.4.2 Data sources

The source of data for continuous surveillance programmes is usually the delivering centre, i.e. the hospital or community pharmacy.

In hospitals, the source of data may be:

1. a business accountancy database, giving information on the number of boxes of antimicrobial products purchased by the hospital during the period under study;

2. a ward delivery database, to determine the number of items or boxes delivered to the different wards;
3. an electronic prescribing database (where such a database exists), containing prescription-related data, such as antimicrobial product, dosage and duration of treatment.

At primary care level, the source of data may be:

1. a business accountancy database in the community pharmacy;
2. a centralized health insurance database, administered by, for example, a government agency, a private business, or a not-for-profit entity;
3. a centralized prescription database, linking information collected from community pharmacies;
4. an electronic prescribing database for general practitioners.

3.4.3 Data types

Health institutions

Two different types of data can be used to monitor antimicrobial consumption in health institutions: the quantity of antimicrobials used and the number of days on treatment.

Community settings

In community settings, it is usually better to measure the quantity of antimicrobials used. Prescription databases are often not available in community pharmacies. Prescription data might be available in countries with a reimbursement scheme, where the information is collected at the pharmacy level. However, even in this case, lack of resources usually does not allow information about duration of treatment, dosage and antimicrobial product to be easily extracted.

3.4.4 Level of detail required (granularity)

Frequency

The frequency of data collection depends on the objectives of the surveillance programme. If the aim is to provide regular figures of antimicrobial consumption at regional or national level, annual or quarterly data are adequate. If the aim is to detect rapid changes in hospital use, as a result of, for instance, policy changes or resistance trends, then a higher frequency, such as monthly, is preferable.

For community pharmacies, quarterly collection could be a good compromise, as it will allow measurement of seasonal variations (winter/summer or dry/rainy periods).

Within-hospital distribution

In hospitals, in addition to measuring overall consumption, it can be useful to categorize the consumption data by ward or unit. Indeed, antimicrobial consumption in intensive care units is usually much higher than in other units.

3.4.5 Data collection

Consumption data

The range of antimicrobials for which information should be collected is shown in Table 3.1.

If data are needed only on the quantity of antimicrobials used, the following information should be collected:

- number of individual items or boxes used;
- product information:
    - active substance (using the ATC classification),
    - content of one item or one box,
    - route of administration.

For data based on prescriptions, the following information should be collected:

- duration of treatment;
- active substance (using the ATC classification);
- daily dose;
- route of administration.

Information on the active substance and the route of administration will allow the number of DDDs to be calculated.

Denominator data

- **Health institutions**

  For health institutions, two denominators can be used: the number of patient-days or the number of admissions.

- **Community pharmacy**

For community pharmacies, the number of inhabitants served can be used as denominator. However, it should be noted that it may be difficult to appraise the population served by the community pharmacy.

3.4.6 Consumption indicators for reporting

The required information on consumption, and the denominator data, should be extracted from the databases at regular intervals (monthly, quarterly or annually). Indicators, such as number of DDDs per 1000 inhabitants per day (for community pharmacies) and DDDs or days of treatment per 100 admissions or 100 patient-days (for health institutions) should be calculated for the reporting period and setting. These calculated indicators should be added to those collected previously to construct a time series. The process can be time-consuming, but its repetitive nature allows it to be easily automated if the data sources are computerized.

3.5 References

1. Ansari F et al. The European surveillance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. *Clin Infect Dis,* 2009; 49: 1496-1504.

2. Zarb P et al. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009. *J Antimicrob Chemother,* 2011; 66:443-449.

3. Zarb P, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): value of a point-prevalence survey of antimicrobial use across Europe. *Drugs,* 2011; 71: 745-755.

4. Amadeo B et al. European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. *J Antimicrob Chemother,* 2010; 65: 2247-2252.

5. *Anatomical Therapeutic Chemical (ATC) classification system: guidelines for ATC classification and DDD assignment.* Oslo, WHO Collaborating Centre for Drug Statistics Methodology, 2011 (http://www.whocc.no/).

4. Collection of point prevalence data on consumption of antimicrobial agents in animals at the farm level

Farmers can be useful sources of data on consumption of antimicrobial agents by animal species, production type and age class. In some countries, farmers are required to maintain records of treatment, which can be a valuable source of data. In other countries, it may be necessary to carry out point prevalence surveys of a sample of farms, which should ideally be representative of the national population. It is also possible to implement longitudinal data collection systems on farms, but this will not be discussed further here. In order to ensure that the sample selected for study is as valid and representative as possible, epidemiological and statistical experts should have an input into the design of the programme. Collecting accurate data is a challenge, and it is important to focus on the most essential information; data collection may need to be limited in order to reduce the demands on the veterinarian or farmer and obtain maximum compliance.

Ideally, the data should be collected routinely as part of an ongoing surveillance programme. Prevalence data can be collected continuously, i.e. for each species each year, or on a rotating basis by species.

4.1 Confidentiality

The confidentiality of individual farm data must be guaranteed, in order to obtain accurate end-use data. Accordingly, the names and addresses of participating farmers should not be revealed to the public. Compliance is likely to be enhanced, and more accurate data recorded, if participants are reassured that the data they supply will not lead to regulatory or other penalties.

4.2 Identification of animal species of concern

In most countries, many species of animals are kept for food production, transportation or companionship. It is often not feasible to include every species in monitoring every year, and it will therefore be necessary to give priority to certain species, e.g. cattle, and production types, e.g. beef, veal or dairy. In assigning priority, account may need to be taken of estimates of the size of the animal population, preliminary data on consumption of antimicrobial agents by species, species-specific rates of carriage of important foodborne pathogens, and other factors that could contribute to the exposure of humans to resistant bacteria. Typically, priority should be given to the animal species and production types that are most important to food production, are suspected to have the

highest rates of exposure to antimicrobial agents, and are known sources of resistant bacteria for humans.

4.3 Farm-level data collection: general considerations

Collection of data from farms can be challenging, and there are a number of barriers to the acquisition of high quality, comprehensive data on antimicrobial consumption. Ideally, accurate, detailed data should be obtained from all farms, but this is usually only possible in the few countries in which reporting of consumption is mandatory and reporting systems are automated. In most countries, end-users do not keep detailed and up-to-date records that are useful for estimation of drug use. Thus, periodic surveys involving the use of questionnaires or other tools are often needed. Most farmers are not trained in veterinary medicine or pharmacology, and many do not clearly distinguish among various types of medication. Consequently, it is often difficult to obtain much more than product label data, from which the interviewer or investigator will need to derive the identity of the antimicrobial agents of interest and other needed information. Except on very small farms, farmers frequently do not know precisely how many animals are on the premises at any one time, or how they are distributed by production type, e.g. cows, calves, heifers, fattening cattle, so it may be necessary to rely on estimates.

It is strongly recommended that pilot studies of farm-level data collection should be undertaken for the most important species, in order to evaluate and refine the methodologies, e.g. farm sampling methods, data collection instruments and validation mechanisms.

4.4 Recruitment of farmers

It is rarely possible, for logistic reasons or because of resource limitations, to include all farmers in a region or country. Some type of sampling is therefore required. Efforts should be made to ensure that the sample of participating farms is representative of the larger population. If an inventory of farms exists, it should be used as a basis for probability-based sampling, e.g. for a given region, selection of a random sample, stratified by farm size for a given species. In most countries, it will be difficult or impossible to obtain registries of farms that can be used for this purpose, and alternative ways of selecting participants, such as non-probability sampling, will be necessary. Options include asking practising veterinarians to identify farms, or soliciting volunteers through notices in trade magazines or abattoirs. It needs to be recognized that such non-probability samples may produce biased estimates. Sampling of farmers should be stratified on the basis of the animal species of concern; consideration should also be given to animal type (e.g. beef or dairy), production type (e.g. intensive or extensive), and farm size (in terms of number of animals). Incentives for participation,

e.g. financial remuneration, may be useful but can result in substantial programme costs. There are obvious advantages to recruiting farmers who maintain good quality records of antimicrobial treatments, as well as animal inventories and records of the dates when animals enter and leave the herd. (This latter information is needed for calculation of treatment rates, etc.) However, the degree to which farms that keep good records are representative of the overall animal production in the country or region should also be considered.

4.5 Data to be collected

As a minimum, the following data should be collected at the farm level for the period of interest (for a point prevalence study, the day of the survey):

- number of treated animals on the farm, by species, age, stage of production and weight in kilograms;
- names of antimicrobial product(s) used for treatment;
- name of the supplier of the product;
- dose;
- dosing interval (per day);
- number of days of treatment;
- route of administration;
- individual or herd treatment; and
- total number of food-producing animals on the farm by species, age, age class and weight.

The first seven items are required to determine the frequency, dose and duration of administration of antimicrobial agents; the last is needed to calculate the prevalence of treatment.

In most countries, farm-level consumption of antimicrobial agents can be divided into routine use, such as growth promotion (where permitted), individual or group-level prophylaxis, and therapy. If possible, the reason for the use of the antimicrobial agents should be recorded.

Groups of antimicrobial agents to be included in the surveillance, and associated ATCvet codes, are shown in Table 4.1. Some antimicrobial growth promoters (AGPs) are not included in the ATCvet system, which was designed for therapeutic use. It is therefore recommended that AGPs belonging to antimicrobial classes included in ATCvet (e.g. tetracyclines) are reported as such, while other AGPs are reported by classes as defined in relevant textbooks (1).

Efforts should be made to record demographic data for the animal population at risk of treatment on the farm. This normally requires collection of data on the general characteristics of the farm (e.g. all livestock on the premises, all livestock owned by the farmer but located on other properties), species, age classes (e.g. piglets, sows, weaner pigs, finishing pigs) and general housing and grouping information (e.g. cows and calves on pasture, broilers in confinement in one barn).

Table 4.1. Groups of veterinary antimicrobial agents that may be included in the surveillance of antimicrobial agents by animal species

Antimicrobial agent group	ATCvet codes
Antimicrobial agents for intestinal use	QA07AA; QA07AB
Antimicrobial agents for intrauterine use	QG01AA; QG01AE; QG01BA; QG01BE QG51AA; QG51AG
Antimicrobial agents for systemic use	QJ01
Antimicrobial agents for intramammary use	QJ51
Antimicrobial agents used as antiparasitic agents	QP51AG

Source: ref 2.

4.6 Methods of data collection

Basic data can be collected from treatment records or through questionnaires. Where possible, in order to avoid extra work for farmers and to minimize recall bias, data should be collected from existing records, which may include electronic or written farm records or on-farm quality assurance programme records. In most cases, however, some additional input from the farmer or a farmworker is required, and this can be a major obstacle to the collection of accurate and representative data. Considerable planning is needed to focus on collecting the most important data, using the methods that are simplest and quickest for the participants, in order to increase the likelihood of obtaining accurate and complete information.

4.6.1 Questionnaires

Questionnaires have the advantages of being relatively simple for the farmer and entailing low costs for administration. They provide data pertaining mainly to treatment prevalence (e.g. the proportion of animals administered a course of treatment during a specified time period) and qualitative data on use (e.g. whether or not a specific antimicrobial agent was used on the study farm during the specified time period and the route of administration). The farmer may fill in the survey form personally, by hand or electronically, or a member of the survey team may conduct an interview by telephone or during a farm visit. Visits are likely to produce more complete information and allow some of the data to be validated, for instance by inspection of facilities, drug storage cabinets and refrigerators. Questionnaires are useful for collection of point prevalence data, such as the number of animals treated the previous day, and information on routine or general treatment practices, farm

characteristics and management practices. Collection of data that vary with time, e.g. therapeutic treatment of individual animals, should be limited to a short and recent interval, e.g. the day of or the week before completion of the questionnaire.

4.6.2 Treatment records

If farms have existing records (e.g. records required by law or for industry quality assurance programmes or farm production records) that contain the desired data, they can ideally be uploaded directly, or used by a member of the survey team to complete the questionnaire, thus saving the farmer time and effort. Informal records (e.g. bills for medicated feed) may also be useful sources of data.

4.7 Farm-level (end-user) point prevalence data collection

Data collection should take into account known seasonal patterns in disease incidence and antimicrobial prescribing practices. Data should be collected separately by food animal species and production type. Some examples for cattle are listed here, but the categorization used should be adapted to the characteristics of animal production in the country. For example, in some countries, dual-purpose cattle production (combined beef and dairy) may be important.

- Cattle – beef
  - cows and bulls,
  - replacement heifers,
  - suckling calves,
  - veal calves,
  - feeder cattle.

- Cattle - dairy
  - lactating cows,
  - dry cows and bulls,
  - replacement heifers,
  - calves.

4.8 References

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2. ESVAC. *Data collection protocol (version 3).* London, European Medicines Agency, 2012 (EMA/85298/2012;

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp).

5. Data management to support integrated surveillance of antimicrobial resistance

This section provides guidelines for data management systems to support integrated surveillance of antimicrobial resistance, and describes software that may be of value to programme coordinators.

5.1 General principles

The core of any programme for surveillance of antimicrobial resistance is an isolate-level database containing relevant details of demographic and microbiological characteristics of samples. As described in Section 1, isolates may be drawn from routine diagnostic work, convenience samples, or controlled studies with defined sampling protocols. Each of these approaches has advantages and disadvantages with regard to clinical relevance, epidemiological value, costs, and sustainability.

Data should be stored in secure databases that permit simple data entry and retrieval, as well as flexible reporting of standard and ad hoc analysis results. Compatibility with similar databases at national and international level is important. In many instances, data are entered manually directly into the surveillance system software. In some cases, a laboratory may already have a data management system or laboratory instrument system for recording of test results. In that case, electronic transfer of results from the routine data management system to the surveillance system is highly recommended, in order to avoid time-consuming and error-prone manual re-entry of existing electronic data.

5.2 Minimal data elements

The elements to be collected in the surveillance programme should reflect the specific scientific and public health objectives, and should take into account the feasibility of consistent collection of the desired fields. Consequently, it is not possible to define a single universal list of minimal data elements. However, this section presents items that can serve as a basis for consideration by programme directors and data managers.

5.2.1 All microbial isolates

Irrespective of the source of a microbial isolate, the following data elements would be useful for inclusion in the surveillance protocol and database design:

- sample information: sample identifier, date of sample collection, type of sample;

- organism results: microbial species and, where relevant, serotype;
- antimicrobial susceptibility test results: susceptibility test method (e.g. disc diffusion, MIC, beta-lactamase, extended spectrum beta-lactamase (ESBL) production), quantitative susceptibility test results (e.g. disc diffusion zone diameters, MIC values), qualitative test interpretations (resistant, intermediate, susceptible, positive, negative);
- any additional relevant laboratory tests performed (e.g. polymerase chain reaction (PCR), pulsed-field gel electrophoresis (PFGE), phage type).

While it is possible to conduct a surveillance programme without quantitative test results, the scientific and epidemiological value of the resulting data will be significantly compromised. Quantitative results give insights into the population ecology and mechanisms of resistance (as well as data quality) that are not possible with test interpretation categories of “resistant”, “intermediate” and “susceptible”. Furthermore, these interpretation categories are generally determined using clinical interpretation breakpoints rather than epidemiological cut-off values, which can mask significant changes in the molecular epidemiology of resistance. Clinical breakpoints may also change over time as knowledge of treatment outcomes improves and dosages change; long-term surveillance should therefore not be linked to breakpoints at a given point in time.

5.2.2 Human isolates

In studies of isolates of bacteria from humans, the study population in most cases is ill individuals presenting to health care centres for diagnosis and therapy. Alternatively, some studies may focus on bacterial colonization or carriage, either in healthy individuals or in patients.

Possible data fields to be considered for inclusion are:

- patient identifiers: medical record number, national identification number, patient name;
- patient demographics: date of birth or age, sex; in some laboratories, it may be relevant to collect information on the person’s race, ethnicity, or nationality;
- patient location: medical ward or clinic where the patient was seen; when relevant, it may also be feasible to capture information on the patient’s place of residence;
- sample indication: as indicated above, human isolates are typically derived from diagnostic samples from ill individuals. However, if the database also includes isolates collected for surveillance or screening purposes, it should be possible to identify these.

5.2.3 Animal isolates

Isolate collection from animals can be much more varied than from humans. Animal isolates may be collected for the diagnosis of sick animals, to satisfy regulatory requirements, or to support defined surveillance protocols, and samples may be collected at many points in the food animal production process.

Possible data fields to be considered for inclusion are:

- animal identifiers: herd identifier, animal identifier;
- animal demographics: animal species, production class;
- animal location (e.g. town, province, farm, clinic, abattoir).

If all isolates in a database have the same general sampling characteristics, this information need not be included in the database at the isolate level. However, it should be available for archival purposes and if data are shared with outside groups unfamiliar with the sampling protocol.

5.2.4 Food isolates

Isolate collection from food sources can be much more varied than from humans. Food isolates may be collected for the investigation of suspected foodborne outbreaks, to satisfy regulatory requirements, or to support defined surveillance protocols. In surveillance programmes exploring the links between antimicrobial resistance elements in food animals and in humans, the focus is generally food of animal origin. In other instances, it may also be of interest to collect samples from food of plant origin.

Possible data fields to be considered for inclusion are:

- food sample identifiers;
- food demographics: animal or plant species;
- food location: location of food collection (e.g. market, home).

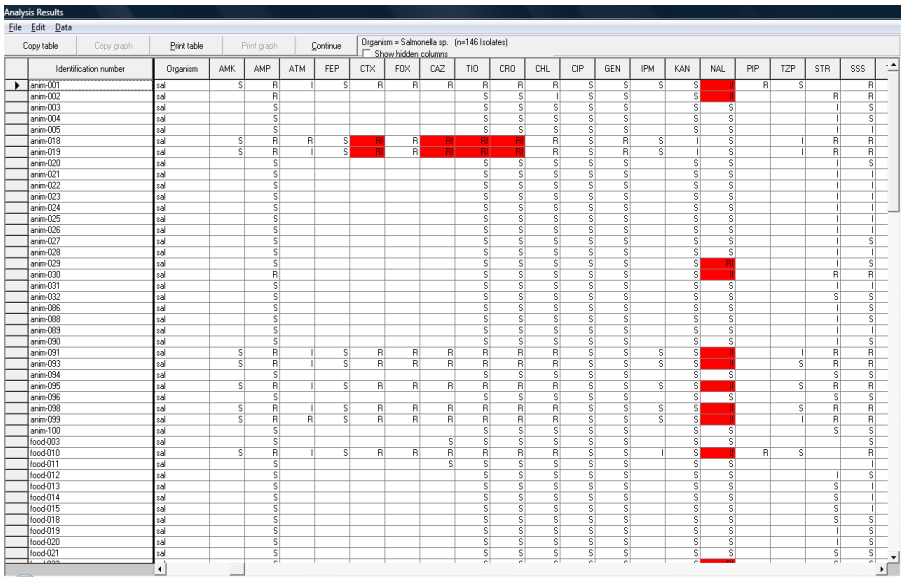
5.3 Examples of data analysis

The data analysis software should have a variety of analysis options to permit the flexible exploration of resistance characteristics and associations. The following are some examples of analyses that could be considered. The examples given here were generated with WHONET (see section 5.4).

5.3.1 Isolate listing and summaries

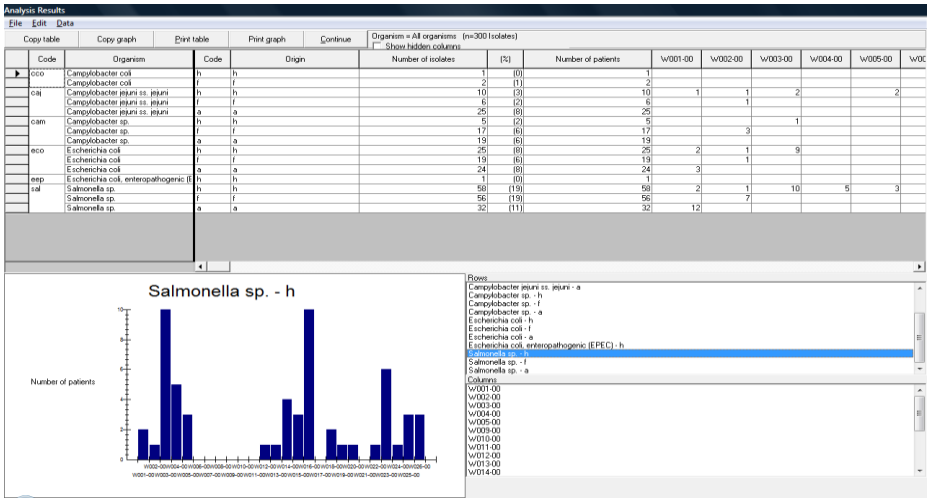
The user should be able to generate a list of isolates with specific sample or microbiological characteristics, e.g. animal species, time of collection, serotype or fluoroquinolone-resistance (Figure 5.1). It would be valuable to have a list of microbiological alerts to identify organisms with unlikely, infrequent, or important resistance phenotypes. These alerts can be predefined for certain findings of known interest or can be based on comparisons with local historical data, to highlight isolates that have not previously been seen in the community.

Figure 5.1. Listing of *Salmonella* isolates from human, animal, and food sources. Important, infrequent, or unlikely resistance findings are highlighted in red, including several strains resistant to nalidixic acid (NAL) and two isolates resistant to third-generation cephalosporins (cefotaxime (CTX), ceftazidime (CAZ), ceftiofur (TIO), ceftriaxone (CRO).



It is also often of interest to summarize lists as statistics that permit organisms to be tracked by time of collection, geographical location, animal species, or other parameters of interest (Figure 5.2).

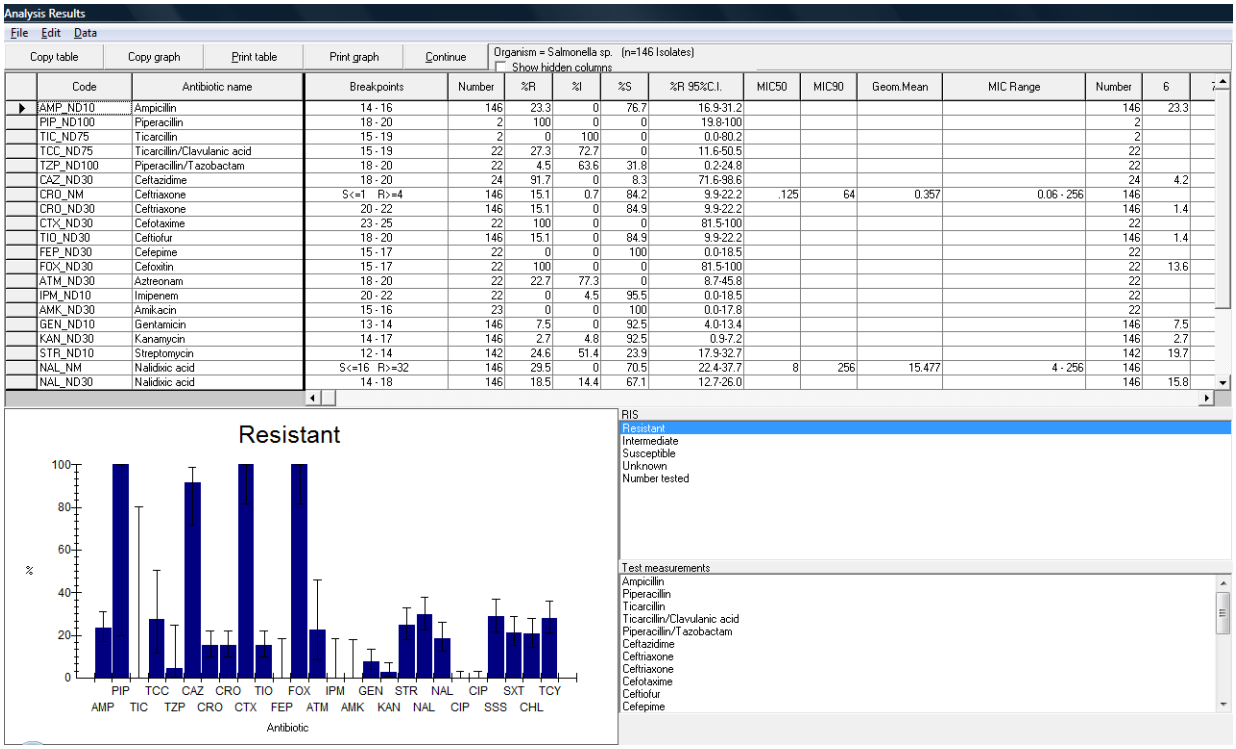
Figure 5.2 isolates by week and by origin of isolate (h = human, a = animal, f = food)



5.3.2 Interpretation categories

The most common way to present the results of antimicrobial susceptibility testing is as percentages of resistant, intermediate, and susceptible (RIS) isolates (Figure 5.3). Such results can be stratified by time of collection, geographical location, animal species, and other characteristics to highlight changes over time or differences in study populations (Figure 5.4).

Figure 5.3 RIS and MIC statistics for *Salmonella* isolates from human, animal, and food samples.



Code	Antibiotic name	Breakpoints	Number	%R	%I	%S	%R 95%C.I.	MIC50	MIC90	Geom.Mean	MIC Range	Number	6
AMP_ND10	Ampicillin	14 - 16	146	23.3	0	76.7	16.9-31.2					146	23.3
PIP_ND100	Piperacillin	18 - 20	2	100	0	0	19.8-100					2	
TIC_ND75	Ticarcillin	15 - 19	2	0	100	0	0.0-80.2					2	
TCC_ND75	Ticarcillin/Clavulanic acid	15 - 19	22	27.3	72.7	0	11.6-50.5					22	
TZP_ND100	Piperacillin/Tazobactam	18 - 20	22	4.5	63.6	31.8	0.2-24.8					22	
CAZ_ND30	Ceftazidime	18 - 20	24	91.7	0	8.3	71.6-98.6					24	4.2
CRO_NM	Ceftriaxone	S<=1 R>=4	146	15.1	0.7	84.2	9.9-22.2	.125	64	0.357	0.06 - 256	146	
CRO_ND30	Ceftriaxone	20 - 22	146	15.1	0	84.9	9.9-22.2					146	1.4
CTX_ND30	Cefotaxime	23 - 25	22	100	0	0	81.5-100					22	
TIO_ND30	Ceftiofur	18 - 20	146	15.1	0	84.9	9.9-22.2					146	1.4
FEP_ND30	Cefepime	15 - 17	22	0	0	100	0.0-18.5					22	
FOX_ND30	Cefoxitin	15 - 17	22	100	0	0	81.5-100					22	13.6
ATM_ND30	Aztreonam	18 - 20	22	22.7	77.3	0	8.7-45.8					22	
IPM_ND10	Imipenem	20 - 22	22	0	4.5	95.5	0.0-18.5					22	
AMK_ND30	Amikacin	15 - 16	23	0	0	100	0.0-17.8					22	
GEN_ND10	Gentamicin	13 - 14	146	7.5	0	92.5	4.0-13.4					146	7.5
KAN_ND30	Kanamycin	14 - 17	146	2.7	4.8	92.5	0.9-7.2					146	2.7
STR_ND10	Streptomycin	12 - 14	142	24.6	51.4	23.9	17.9-32.7					142	19.7
NAL_NM	Nalidixic acid	S<=16 R>=32	146	29.5	0	70.5	22.4-37.7	8	256	15.477	4 - 256	146	
NAL_ND30	Nalidixic acid	14 - 18	146	18.5	14.4	67.1	12.7-26.0					146	15.8

Figure 5.4 RIS and MIC results for *Salmonella* spp stratified by origin of isolate

Antibiotic name	Origin	Breakpoints	Number	%R	%I	%S	%R 95%C.I.	MIC50	MIC90	Geom.Mean	MIC Range
Disk diffusion results											
Ampicillin	Animal	14 - 16	32	31.2	0	68.8	16.7-50.1				
Ampicillin	Food	14 - 16	56	8.9	0	91.1	3.3-20.3				
Ampicillin	Human	14 - 16	58	32.8	0	67.2	21.4-46.5				
Ceftiofur	Animal	18 - 20	32	25	0	75	12.1-43.8				
Ceftiofur	Food	18 - 20	56	1.8	0	98.2	0.1-10.8				
Ceftiofur	Human	18 - 20	58	22.4	0	77.6	12.9-35.6				
Ciprofloxacin	Animal	16 - 20	32	0	0	100	0.0-13.3				
Ciprofloxacin	Food	16 - 20	56	0	0	100	0.0-8.0				
Ciprofloxacin	Human	16 - 20	58	0	0	100	0.0-7.7				
Gentamicin	Animal	13 - 14	32	6.2	0	93.8	1.1-22.2				
Gentamicin	Food	13 - 14	56	0	0	100	0.0-8.0				
Gentamicin	Human	13 - 14	58	15.5	0	84.5	7.8-27.9				
Nalidixic acid	Animal	14 - 18	32	3.1	25	71.9	0.2-18.0				
Nalidixic acid	Food	14 - 18	56	30.4	7.1	62.5	19.2-44.3				
Nalidixic acid	Human	14 - 18	58	15.5	15.5	69	7.8-27.9				
Trim/Sulfa	Animal	11 - 15	32	15.6	0	84.4	5.9-33.5				
Trim/Sulfa	Food	11 - 15	56	10.7	0	89.3	4.4-22.5				
Trim/Sulfa	Human	11 - 15	58	34.5	1.7	63.8	22.8-48.2				
MIC results											
Ciprofloxacin	Animal	S<=1 R>=4	32	0	0	100	0.0-13.3	0.032	0.125	0.055	0.03 - 0.5
Ciprofloxacin	Food	S<=1 R>=4	56	0	0	100	0.0-8.0	0.064	0.5	0.088	0.03 - 1
Ciprofloxacin	Human	S<=1 R>=4	58	0	0	100	0.0-7.7	0.064	0.25	0.075	0.03 - 0.5
Nalidixic acid	Animal	S<=16 R>=32	32	21.9	0	78.1	10.0-40.5	8	32	9.935	4 - >128
Nalidixic acid	Food	S<=16 R>=32	56	33.9	0	66.1	22.1-47.9	8	256	24.372	4 - >128
Nalidixic acid	Human	S<=16 R>=32	58	29.3	0	70.7	18.5-42.9	8	32	12.75	4 - >128

Most commonly, categories are determined using clinical interpretative guidelines, as published by CLSI or EUCAST. However, interpretation of results in terms of epidemiological cutoff values can provide a more accurate estimate of the emergence of resistance elements in a study population than therapy-based predictors of clinical efficacy. To permit flexibility in the analysis of results, a valuable feature of the software is the ability to generate category interpretations dynamically at the time of analysis, to accommodate the application of both clinical and epidemiological breakpoints, EUCAST and CLSI interpretation criteria, and updated interpretations for historical data. CLSI recommends that, in the absence of changes to the susceptibility test methodology, test results, even for historical data, should be interpreted using recent breakpoints, rather than the breakpoints at the time the test was originally performed (1). The rationale for this recommendation is that newer breakpoints more accurately reflect current understanding of clinical test interpretation.

5.3.3 Test measurements

Quantitative susceptibility test results, specifically disc diffusion zones of inhibition and MIC values, provide much greater insight into the molecular epidemiology of resistance characteristics than simple categorical interpretations of resistant, intermediate, and susceptible. Quantitative measurements have a number of critical benefits:

- they allow evaluation of data quality;

- they allow flexible analysis and re-analysis of data using different interpretation guidelines (CLSI vs EUCAST, clinical vs epidemiological criteria, changes in interpretative guidelines over time);
- resistance mechanisms can be characterized by level of resistance; a new appearance of low-level resistance can be detected, which may be missed if clinical breakpoints are used;
- they discriminate between microbial subpopulations;
- they allow evaluation of the adequacy and robustness of reference interpretation criteria.

Results may be depicted graphically, as in Figures 5.5 and 5.6, or in tabular format (Tables 5.1 and 5.2).

Figure 5.5 Disk diffusion zone diameters of inhibition around the ceftiofur antimicrobial disc for isolates of *Salmonella* spp. The graph shows that there are at least three distinctive *Salmonella* strain phenotypes in the study population: (1) a susceptible population to the right of the cut-off values, (2) a group with high-level resistance (6mm zone diameter) to the far left, and (3) a group of strains with low to moderate levels of resistance, just to the left of the resistant breakpoint.

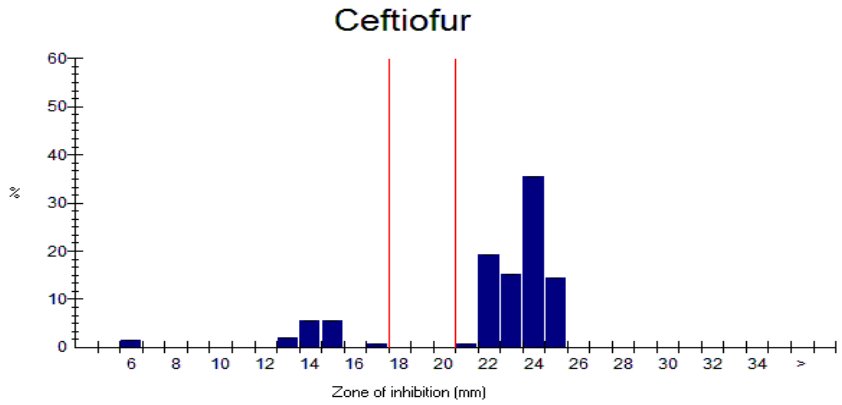


Figure 5.6 Ceftriaxone MIC values for isolates of *Salmonella spp.* The graph shows that there are at least three distinctive *Salmonella* strain phenotypes in the study population: (1) a susceptible population to the left of the cut-off values, (2) a resistant group to the right of the graph, and (3) a small group in the intermediate category (between the interpretative criteria lines).

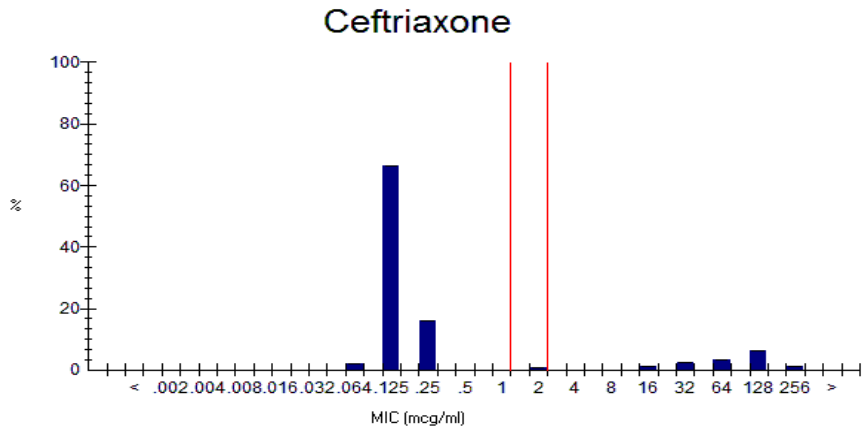


Table 5.1. Quantitative disc diffusion distribution for human, animal, and food isolates of *Salmonella* spp.

Antibiotic name	Origin	Number	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	>35
Ampicillin	Animal	32	31															3	34	22	6	3											
	Food	56	9															4	23	29	29	7											
	Human	58	33															7	19	21	16	5											
Ceftiofur	Animal	32								9	13	3							34	16	16	9											
	Food	56									2								18	16	46	18											
	Human	58	3								5	12		2				2	12	14	36	14											
Ciprofloxacin	Animal	32																			3		3	9	9	9	25	34	6			
	Food	56																		2	4		11	9	16	13	11	14	21			
	Human	58																			2	2	2	3	10	16	9	19	14	3	17	3
Gentamicin	Animal	32	6												41	47		3								3						
	Food	56												2	16	63	9	7	4													
	Human	58	16									3	2		12	22	9	29	2	2		2			2							
Nalidixic acid	Animal	32	3								9	3	13					3	50	9	9											
	Food	56	30									2	2		4	2		2	34	2	21	2											
	Human	58	9							7	12	2			2	2	2	16	35	10	5											
Trim/Sulfa	Animal	32	16											9	6							25	31	13								
	Food	56	11																2			21	48	7	9	2						
	Human	58	35						2										3	2	12	19	14	12	2							

Table 5.2. Quantitative MIC distribution for human, animal, and food isolates of *Salmonella* sp.

Antibiotic name	Origin	Number	0.03	0.06	0.13	0.25	0.5	1	2	4	8	16	32	64	128	>256
Ceftriaxone	Animal	32		9	34	31						6	9	6	3	
	Food	56			91	7									2	
	Human	58			60	16			2				2	5	12	3
Ciprofloxacin	Animal	32	50	25	16	6	3									
	Food	56	29	34	7	20	7	4								
	Human	58	28	31	29	7	5									
Nalidixic acid	Animal	32								31	38	9	19			3
	Food	56								13	45	9	2			32
	Human	58								22	43	5	21			9

While MIC statistics are less informative than full measurement distribution displays, they can usefully be summarized using MIC_{50}, MIC_{90}, MIC range, and MIC geometric mean (see Figure 5.4).

5.3.4 Co-resistance and cross-resistance

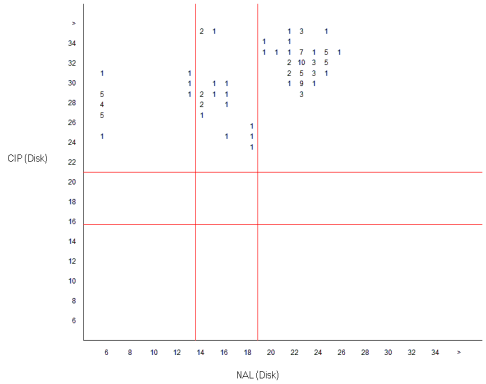
The displays in the previous section highlight resistance findings for individual antibiotics. The exploration of correlation of resistance findings between two or more antimicrobials is also of interest. This section describes comparison of findings between two antimicrobial agents or test methods, while section 5.3.5 deals with comparison of findings among multiple agents.

- Co-resistance is resistance to more than one antimicrobial agent of the same or different classes.
- Cross-resistance is a specific type of co-resistance, in which resistance can be attributed to a single genetic mechanism. Cross-resistance is commonly seen within an antimicrobial class; for example, strains resistant to ceftriaxone are typically also resistant to cefotaxime and are frequently resistant to ceftazidime. Cross-resistance between antimicrobial classes can also be seen, where there is a common target site of antimicrobial action. For example, staphylococcal isolates with modified ribosomes may display simultaneous resistance to macrolides, lincosamides, and streptogramin B, recognized as an MLS_B phenotype.

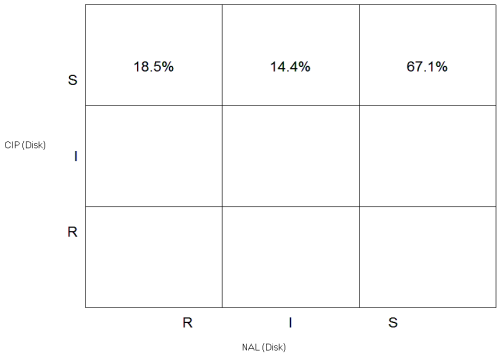
A quantitative scatterplot of test measurements (Figure 5.7) offers greater discrimination of resistance phenotypes and microbial subpopulations than is possible when only a single antimicrobial is studied. A qualitative scatterplot, based on interpretation categories, can help evaluate the relative efficacy of similar or distinct antimicrobial agents, providing information of value to pharmacists and policy-makers in the consideration of treatment alternatives.

Figure 5.7 Quantitative and qualitative scatterplots of *Salmonella* isolates, comparing nalidixic acid and ciprofloxacin (7a and 7b) and ampicillin and ceftriaxone (7c and 7d). The graphs show that test

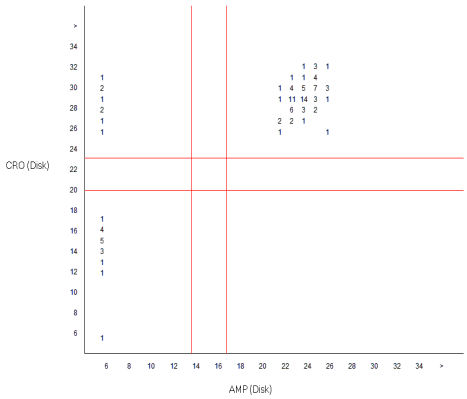
measurements permit much finer discrimination of resistance mechanisms and phenotypic subpopulations than is possible with interpretation categories.



7a.

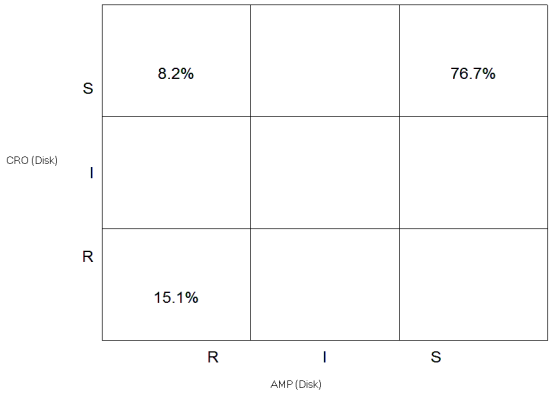


7b.



7c.

7d.



Scatterplots can also be useful in showing correlations between test findings, even for a single antimicrobial agent; for example, disc diffusion zone diameters for imipenem can be compared with MIC values for the same agent. Such analyses are used in establishing interpretation criteria, to document how well different test methods can detect resistance (Figure 5.8).

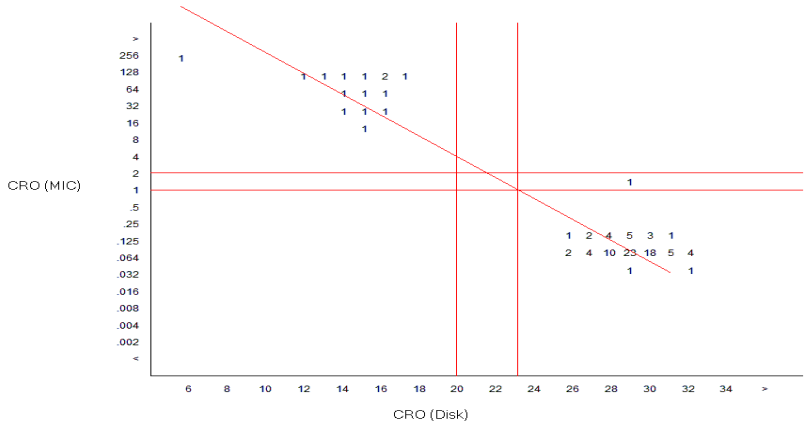


Figure 5.8 Scatterplot comparison of disc diffusion diameters and MIC values for susceptibility of *Salmonella* isolates to ceftriaxone

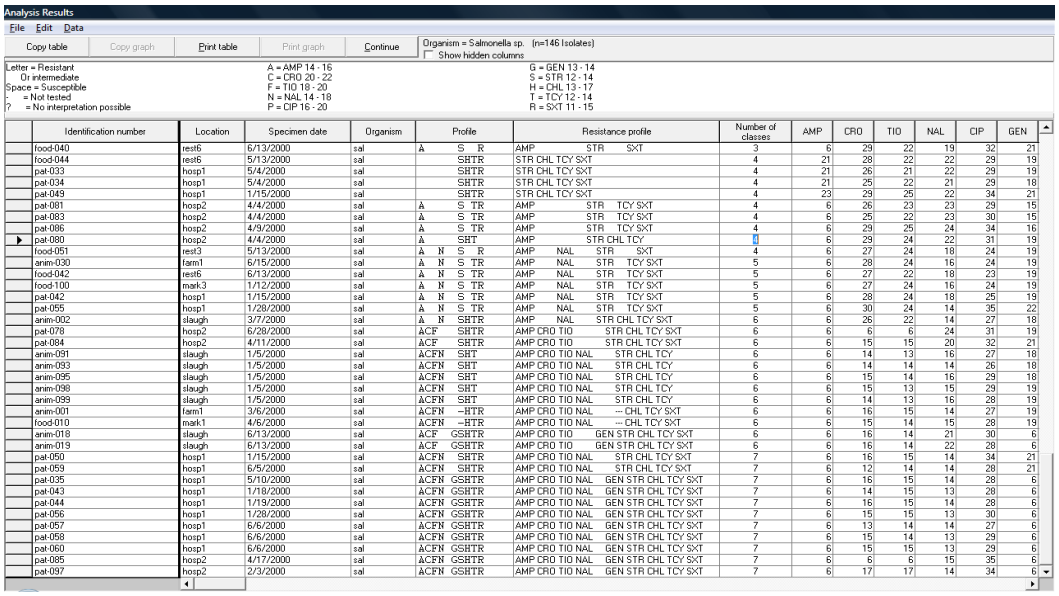
5.3.5 Multidrug resistance

The comparison of test results for a number of antimicrobials can provide improved characterization of resistance mechanisms and refine the discrimination of phenotypic subpopulations.

- Resistance mechanisms. By studying patterns of resistance to agents in a single antimicrobial class, such as aminoglycosides, it is often possible to identify possible genetic elements consistent with the observed phenotype, especially when the level of resistance (borderline, moderate or high) is taken into account. It is also possible to identify potential quality assurance issues, if unlikely phenotypes are identified, e.g. a strain resistant to ciprofloxacin but susceptible to nalidixic acid.
- Therapeutic alternatives. Studies of multidrug resistance can highlight the clinical efficacy of possible treatment options; for example, it would be possible to examine what proportion of *Campylobacter* isolates in a particular geographical area are resistant to all agents routinely used in the management of campylobacteriosis.
- Phenotypic markers of microbial subpopulations. State-of-the-art typing strategies include genetic characterization, such as full-genome sequencing or multi-locus sequence typing (MLST). However, such methods are generally expensive and time-consuming, and are not routinely available to support outbreak detection efforts in real time. Studies of phenotypic characteristics, such as antimicrobial resistance patterns, can facilitate the recognition of outbreaks and important clones.

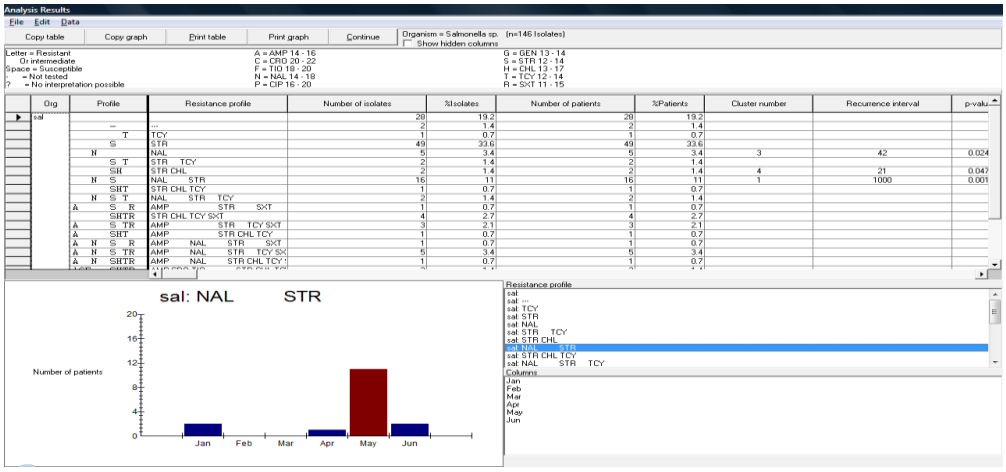
Resistance profiles can be integrated into listings of isolate results, as in Figure 5.9 or summarized in aggregate form, for example by time (Figure 5.10), by geographical location, by animal species, or by serotype.

Figure 5.9 Listing of isolates with resistance profiles. The column labelled “Resistance profile” shows the agents to which the isolate is not susceptible (resistant or intermediate). Isolates at the top of the listing are resistant to four agents; the most resistant isolates, which were not susceptible to nine antimicrobial agents, appear at the bottom of the list.



Identification number	Location	Specimen date	Organism	Profile	Resistance profile	Number of classes	AMP	CRO	TIO	NAL	CIP	GEN
food-040	rest6	6/13/2000	sal	A S R	AMP STR SXT	3	6	29	22	19	32	21
food-044	rest6	5/13/2000	sal	SHTR	STR CHL TCY SXT	4	21	28	22	22	29	19
pat-033	hosp1	5/4/2000	sal	SHTR	STR CHL TCY SXT	4	21	26	21	22	29	19
pat-034	hosp1	5/4/2000	sal	SHTR	STR CHL TCY SXT	4	21	25	22	21	29	18
pat-049	hosp1	1/15/2000	sal	SHTR	STR CHL TCY SXT	4	23	29	25	22	34	21
pat-081	hosp2	4/4/2000	sal	A S TR	AMP STR TCY SXT	4	6	26	23	23	29	15
pat-083	hosp2	4/4/2000	sal	A S TR	AMP STR TCY SXT	4	6	25	22	23	30	15
pat-086	hosp2	4/9/2000	sal	A S TR	AMP STR TCY SXT	4	6	29	25	24	34	16
pat-080	hosp2	4/4/2000	sal	A SHT	AMP STR CHL TCY	4	6	29	24	22	31	19
food-051	rest3	5/13/2000	sal	A N S R	AMP NAL STR SXT	4	6	27	24	18	24	19
anim-030	farm1	6/15/2000	sal	A N S TR	AMP NAL STR TCY SXT	5	6	28	24	16	24	19
food-042	rest6	6/13/2000	sal	A N S TR	AMP NAL STR TCY SXT	5	6	27	22	18	23	19
food-100	mark3	1/12/2000	sal	A N S TR	AMP NAL STR TCY SXT	5	6	27	24	16	24	19
pat-042	hosp1	1/15/2000	sal	A N S TR	AMP NAL STR TCY SXT	5	6	28	24	18	25	19
pat-055	hosp1	1/28/2000	sal	A N S TR	AMP NAL STR TCY SXT	5	6	30	24	14	35	22
anim-002	slaugh	3/7/2000	sal	A N SHTR	AMP NAL STR CHL TCY SXT	6	6	26	22	14	27	18
pat-078	hosp2	6/28/2000	sal	ACF SHTR	AMP CRO TIO STR CHL TCY SXT	6	6	6	6	24	31	19
pat-084	hosp2	4/11/2000	sal	ACF SHTR	AMP CRO TIO STR CHL TCY SXT	6	6	15	15	20	32	21
anim-091	slaugh	1/5/2000	sal	ACFN SHT	AMP CRO TIO NAL STR CHL TCY	6	6	14	13	16	27	18
anim-093	slaugh	1/5/2000	sal	ACFN SHT	AMP CRO TIO NAL STR CHL TCY	6	6	14	14	14	26	18
anim-095	slaugh	1/5/2000	sal	ACFN SHT	AMP CRO TIO NAL STR CHL TCY	6	6	15	14	16	29	18
anim-098	slaugh	1/5/2000	sal	ACFN SHT	AMP CRO TIO NAL STR CHL TCY	6	6	15	13	15	29	19
anim-099	slaugh	1/5/2000	sal	ACFN SHT	AMP CRO TIO NAL STR CHL TCY	6	6	14	13	16	28	19
anim-001	farm1	3/6/2000	sal	ACFN --HTR	AMP CRO TIO NAL --- CHL TCY SXT	6	6	16	15	14	27	19
food-010	mark1	4/6/2000	sal	ACFN --HTR	AMP CRO TIO NAL --- CHL TCY SXT	6	6	15	14	15	28	19
anim-018	slaugh	6/13/2000	sal	ACF GSHTR	AMP CRO TIO GEN STR CHL TCY SXT	6	6	16	14	21	30	6
anim-019	slaugh	6/13/2000	sal	ACF GSHTR	AMP CRO TIO GEN STR CHL TCY SXT	6	6	16	14	22	28	6
pat-050	hosp1	1/15/2000	sal	ACFN SHTR	AMP CRO TIO NAL STR CHL TCY SXT	7	6	16	15	14	34	21
pat-059	hosp1	6/5/2000	sal	ACFN SHTR	AMP CRO TIO NAL STR CHL TCY SXT	7	6	12	14	14	28	21
pat-035	hosp1	5/10/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	16	15	14	28	6
pat-043	hosp1	1/18/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	14	15	13	28	6
pat-044	hosp1	1/19/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	16	15	14	28	6
pat-056	hosp1	1/28/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	15	15	13	30	6
pat-057	hosp1	6/6/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	13	14	14	27	6
pat-058	hosp1	6/6/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	15	14	13	29	6
pat-060	hosp1	6/6/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	15	15	13	29	6
pat-085	hosp2	4/17/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	6	6	15	35	6
pat-097	hosp2	2/3/2000	sal	ACFN GSHTR	AMP CRO TIO NAL GEN STR CHL TCY SXT	7	6	17	17	14	34	6

Figure 5.10 Summary of resistance profiles shown in Figure 5.9. The most common resistance profile observed in the study population was non-susceptibility to streptomycin. The graph depicts a possible outbreak of *Salmonella* non-susceptible to both nalidixic acid and streptomycin.



5.4 Software tools

Although the epidemiology of antimicrobial resistance displays considerable variety and complexity, the core of any database for a resistance surveillance programme is the identity of the microbial isolates, their antimicrobial susceptibility test results, and relevant descriptive information on the source.

5.4.1 WHONET

WHONET is a freely available software for the management of microbiology test results, developed and supported since 1989 by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance at the Brigham and Women's Hospital in Boston, United States of America. The software is currently in use in hospital, public health, veterinary, and food laboratories in over 110 countries, and is available in over 20 languages. The software and educational tutorials can be downloaded from www.whonet.org.

The software includes the following modules.

- Laboratory configuration: characteristics of the laboratory; antimicrobials tested; locations for monitoring of human isolates (e.g. hospital wards, clinics, communities); locations for monitoring of animal isolates (e.g. farms, abattoirs, zoos); locations for monitoring of food isolates (e.g. markets, restaurants); and configurable lists of optional data fields to be used for data entry.
- Data entry: the user enters information on the human, animal, or food subject of study, relevant demographic and location details, sample information, microbial species, antimicrobial susceptibility test results, and any additional available demographic, clinical or molecular details desired.
- Data analysis: several analysis options were described in section 5.3; they include isolate listings and summaries, percentage RIS isolates, test measurement statistics, scatterplots, multidrug resistance profiles, and statistical and microbiological alerts to possible outbreaks and important or unusual laboratory findings. Results can be saved as Microsoft Excel or Access files, which is particularly convenient when WHONET is run in automated batch mode.
- BacLink: this is the data import module for WHONET, which allows data to be transferred electronically, rather than entered manually. Sources of data may include computer applications (Microsoft Excel, Microsoft Access, text files), laboratory test instruments, or commercial or in-house developed laboratory information systems.

5.5 Reference

1. *Analysis and presentation of cumulative antimicrobial susceptibility test data.* Wayne, PA, Clinical and Laboratory Standards Institute, 2009 (document M39-A3).

6. Data management to support integrated surveillance of antimicrobial consumption

6.1 General principles

There are a number of ways to document antimicrobial use and a number of possible data sources. As a result, data on antimicrobial use vary greatly in granularity (individual pills vs. patient prescriptions vs. aggregate statistics), type (antimicrobials purchased, dispensed or administered) and antimicrobial use scenario (therapeutic, prophylactic or growth promotion). There is also a wide range of potentially useful additional information relevant to understanding the decision to use a particular antimicrobial, such as clinical diagnosis, supportive diagnostic test results, patient expectations and financial considerations. Consequently, database design and needs for data management, analysis, and presentation can be very different from project to project.

This section presents some guidelines on data management in support of the recommendations in sections 3 and 4. There are two primary and complementary strategies that can be used to track antimicrobial use:

- quantitative: the quantity of antimicrobials used; valuable for tracking the total antimicrobial use in different populations and over time;
- qualitative: why and how antimicrobials are used; valuable for understanding the factors that contribute to the decision to use an antimicrobial, as well as the appropriateness of such use.

Both approaches can be applied to monitor antimicrobial use in health care facilities, farms, provinces, and countries, and have been successfully used to track the impact of educational and regulatory interventions on antimicrobial use patterns.

Antibiotic use in animals or in the food chain may be a major driver of antimicrobial resistance in developing countries, but the variety of supply sources there may make such use more difficult to measure. It might be helpful to develop software to facilitate "snapshot" surveys of antibiotic use on representative farms, analogous to that developed for one-time, point prevalence surveys of antimicrobial use in individual hospitals (see section 3.2).

6.1.1 Quantitative antimicrobial use

This approach attempts to track total quantities of antimicrobials used at local, regional, or national level. Depending on the data sources available, quantities may be expressed in terms of economic cost, total weight, DDDs, days of treatment or other measures of total use. In some instances, the database may contain information at the patient or animal level, such as number of pills dispensed or prescribed. From such granular details, aggregate statistics can be calculated. In other cases, the only data available may be aggregate statistics, such as number of packages of a particular antibiotic purchased by a health clinic in a given period.

Chapters 3 and 4 provide a template for the presentation of national aggregate statistics. For surveillance of antimicrobial use in both human and animal populations, recommended data fields include:

- sample population: country, year, animal species (if available);
- period covered (year, quarter, month);
- identity of antimicrobial: medicinal product identifier code, name or label;
- active substance: name, ATC code, ATC DDD;
- package content: quantity (including quantity of active ingredients), units of measurement of active ingredients, number of items per package and, where relevant, conversion factor for associated salts and prodrugs;
- administration: pharmaceutical form, route of administration;
- consumption: number of packages used (sold, prescribed, reimbursed, delivered), duration of treatment;
- statistics derived from the above:
    - number of kg of drug used,
    - number of DDDs,
    - number of days of treatment.

6.1.2 Qualitative antimicrobial use

Understanding how and why antimicrobials are used is a more complicated issue than simply estimating the amount used. Despite this complexity, it is often simpler and more feasible to collect qualitative survey “snapshots” of antimicrobial use. Often, aggregate data on antimicrobial use do not exist or are not made available to public health authorities by insurance systems or commercial entities, such as pharmaceutical companies and food producers.

A useful series of documents has been developed and validated over time by WHO in collaboration with many international partners, to help guide the collection of data on antimicrobial use in a variety of clinical and non-clinical settings (1-4). The use of drug use indicators has proven to be a simple but valuable tool for highlighting deficiencies and prioritizing interventions in drug procurement, compliance with standard treatment guidelines, and the education of health care workers. In addition, section 3.2 contains recommendations for monitoring antimicrobial use in hospitals.

6.2 Examples of data analysis

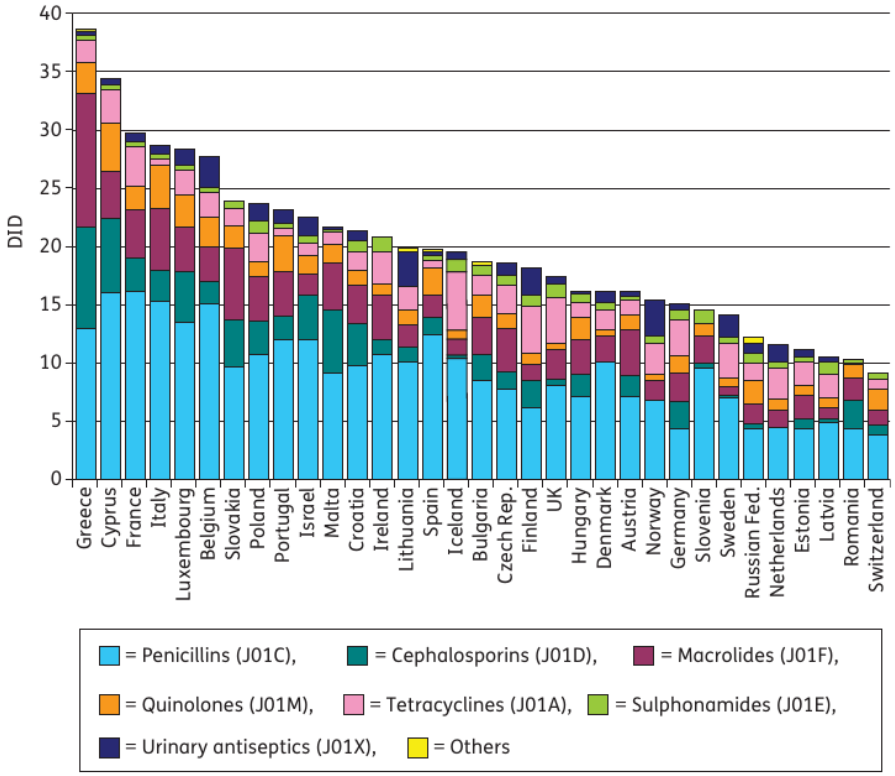
In collaboration with a number of partners, including the International Network for Rational Use of Drugs (INRUD), WHO has for many years supported drug use surveys in a variety of clinical and non-clinical settings, especially in low-resource countries. Some of the best models have been pioneered through European initiatives, most notably European Surveillance of Antimicrobial Consumption (ESAC) and, more recently, European Surveillance of Veterinary Antimicrobial Consumption (ESVAC).

6.2.1 Aggregate statistics on antimicrobial use

ESAC was established in 2001 and collected aggregate statistics on the use of antimicrobials in the participating countries. From 2001 to 2011, the project included 35 countries. In 2011, the surveillance programme was transferred to the European Centre for Disease Prevention and Control (ECDC) and renamed ESAC-Net. On an annual basis, each participating country collates aggregate statistics (reimbursement data or sales data) on the national consumption of antimicrobials from a variety of databases. Consumption is expressed in terms of number of packages or, if not available, as number of DDDs at the substance level. Separate data are presented for antimicrobial use in hospitals and in community settings. Significant efforts have been made to standardize protocols, definitions and data types. For most countries, the statistics reflect the amount of antimicrobials purchased or reimbursed. Departures from the recommended protocol are described in the annual reports. Results are available to the general public on the ECDC website (http://ecdc.europa.eu/en/activities/surveillance/ESAC-Net/database/Pages/database.aspx).

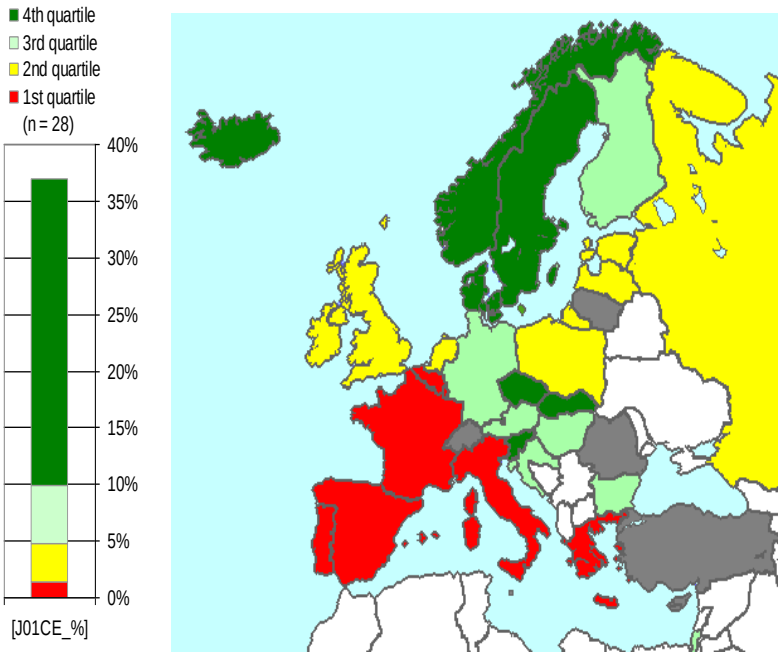
Figure 6.1 shows the significant differences in patterns of antimicrobial use across Europe, both in total volume and in the distribution by antimicrobial class. Figure 6.2 shows similar information for penicillins.

Figure 6.1 Total outpatient antimicrobial use in 33 European countries in 2009, expressed in DDD per 1000 inhabitant-days



Source: 6.

Figure 6.2 Use of narrow-spectrum penicillins (J01CE) as percentage of total antimicrobial consumption in Europe.



Figures 6.3 and 6.4 show how ESAC data have been used to track changes in antimicrobial use over time.

Figure 6.3 Change in outpatient antimicrobial use in Belgium, 1997–2004.

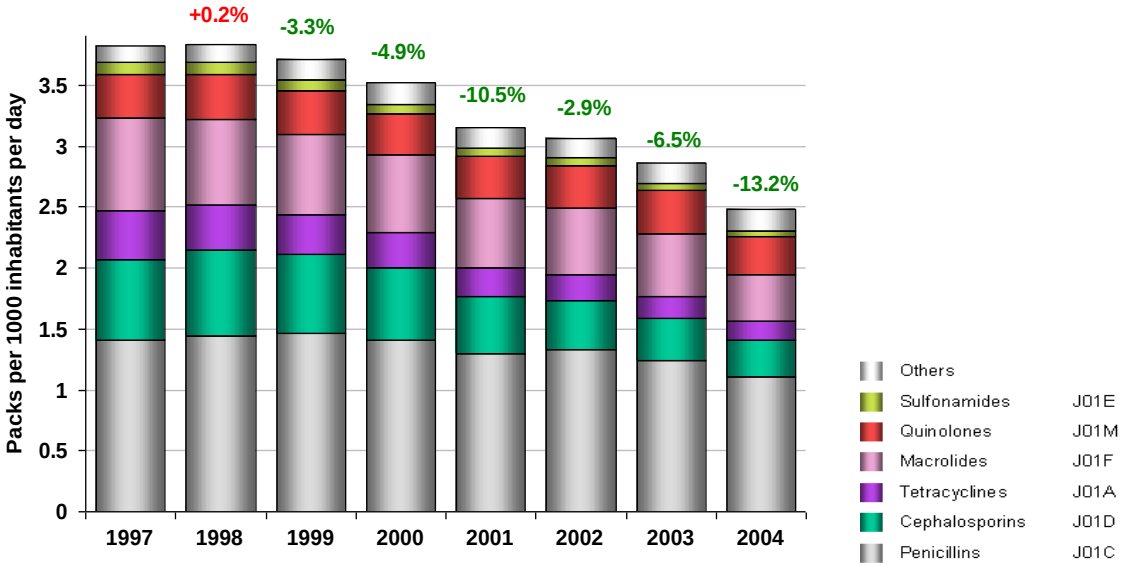
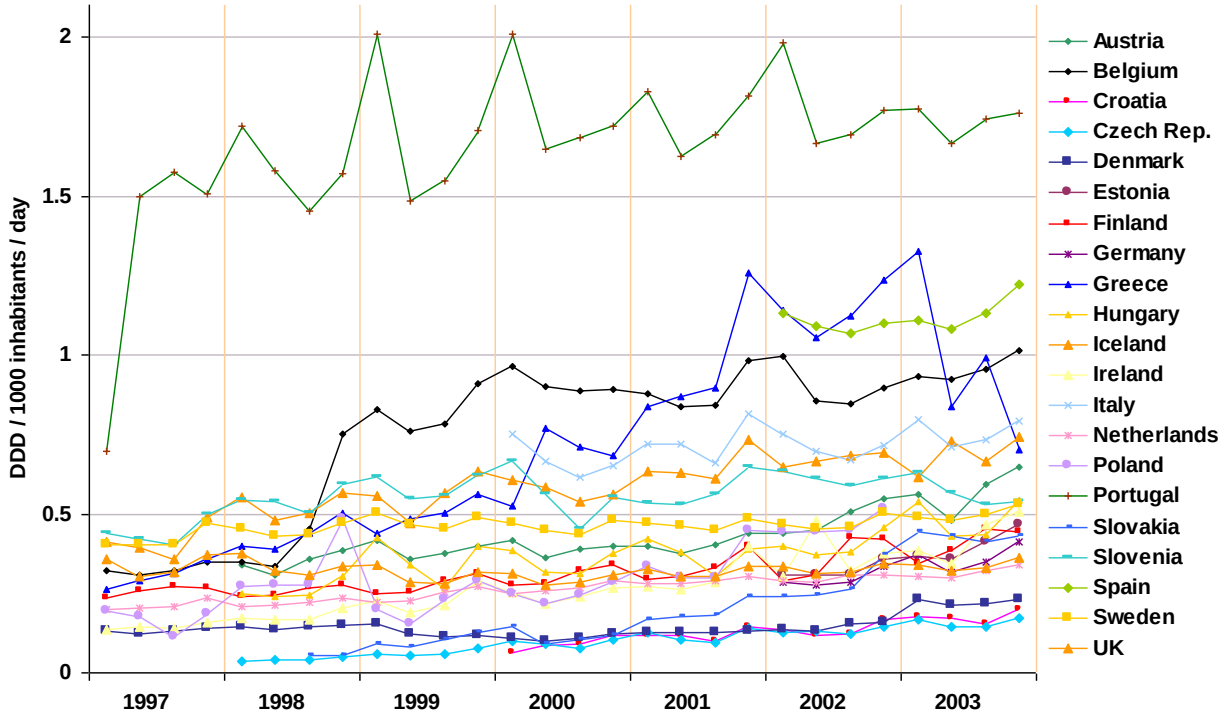


Figure 6.4 Seasonal variation in outpatient ciprofloxacin use, 1997–2003



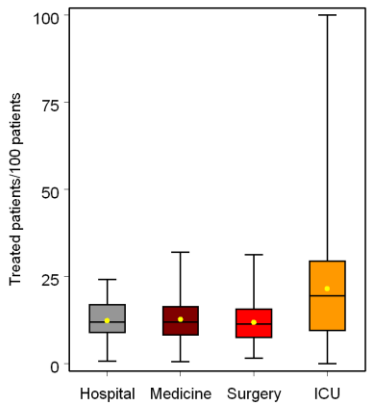
The ESVAC project run by the European Medicines Agency has developed a similar protocol for the collection of aggregate statistics on sales of antimicrobials intended for animals. In 2011, ESVAC collected retrospective data from nine European countries that had comparable surveillance systems in place (7). In October 2012, ESVAC has released a report on Sales of veterinary antimicrobial agents in 19 EU/EEA countries in 2010)

6.2.2 Antimicrobial use surveys

In 2005, the World Health Assembly adopted a resolution entitled "Antimicrobial resistance: a threat to global health security. Rational use of medicines by prescribers and patients" (WHA resolution A58/14). In support of this resolution, WHO assembled an extensive list of surveys of antimicrobial use in patients from all regions of the world (8). Results of indicator studies were published in a number of WHO documents (9, 10).

As an example of regionally coordinated antimicrobial use surveys, section 3.2 provided a brief description of results from an ESAC-led hospital point prevalence survey. This was initiated in 2006 as a pilot project with 20 hospitals in 20 countries. By 2009, point prevalence surveys had been submitted by 172 hospitals (see Figure 6.5). In 2010, the ESAC PPS protocol was adapted and merged with an ECDC protocol for surveying health care-associated infections.

Figure 6.5 Overall proportion of patients treated with antimicrobials by speciality in the ESAC Hospital Point Prevalence Study, 2009.



6.3 Software tools

The data management needs for antimicrobial use programmes are more diverse than those for antimicrobial resistance studies, reflecting the variety of data sources and antimicrobial use settings and indications. Consequently, there is no single software that can handle all these needs, and many initiatives rely on locally developed or customized data solutions.

Nevertheless, the growing acceptance of certain models for monitoring programmes should facilitate the development of new software targeted to these standardized protocols. This section gives some examples of what has been accomplished in specific surveillance projects.

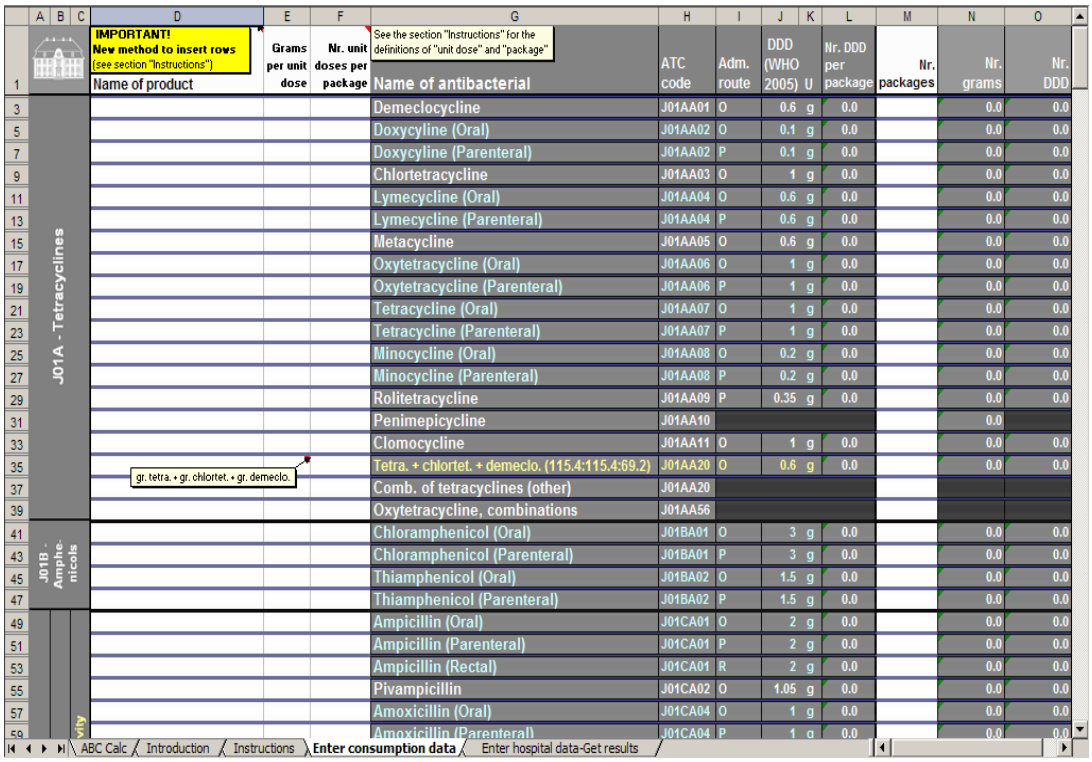
6.3.1 ABC Calc

Many investigators have successfully used the ABC Calc software[1] for monitoring aggregate use statistics at ward, facility, or national level. The current distribution version of ABC Calc is implemented within Microsoft Excel, and relies on predefined formulas and reference values such as ATC classification and DDD definitions. A new Java-based version of ABC Calc is under development.

The data management strategy of ABC Calc closely follows the recommendations for aggregate statistic monitoring described in section 6.1.1. The data entry screen for the current Excel software is shown in Figure 6.6. The user indicates the name of the pharmaceutical product and product details, including the active ingredient and, if relevant, the administration route, the amount of active ingredient per unit, the number of units per package, and the total number of packages purchased or consumed. ABC Calc then automatically generates the total number of kilograms of antibiotic used and, when definitions exist, the number of DDDs.

[1] Available from the European Society of Clinical Microbiology and Infectious Diseases (www.escmid.org/research_projects/study_groups/esgap/abc_calc).

Figure 6.6 ABC Calc data entry screen. The user enters information in the white columns: name of product, grams per unit dose, number of unit doses per package, and number of packages.



6.3.2 ESAC WebPPS

The ESAC project developed a Web- based application for data entry and reporting of its hospital point prevalence surveys. Each participating hospital was asked to register and to enter their data in the application (Figure 6.7). The hospitals were then able to consult automated online reports, as shown in Figure 6.8.

Figure 6.7 ESAC WebPPS data entry for hospital point-prevalence surveys

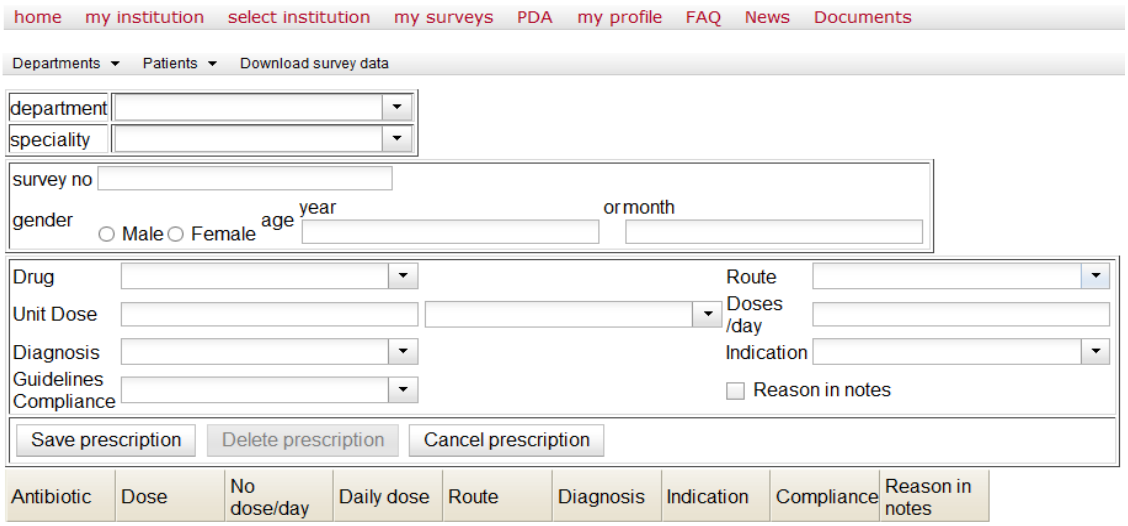
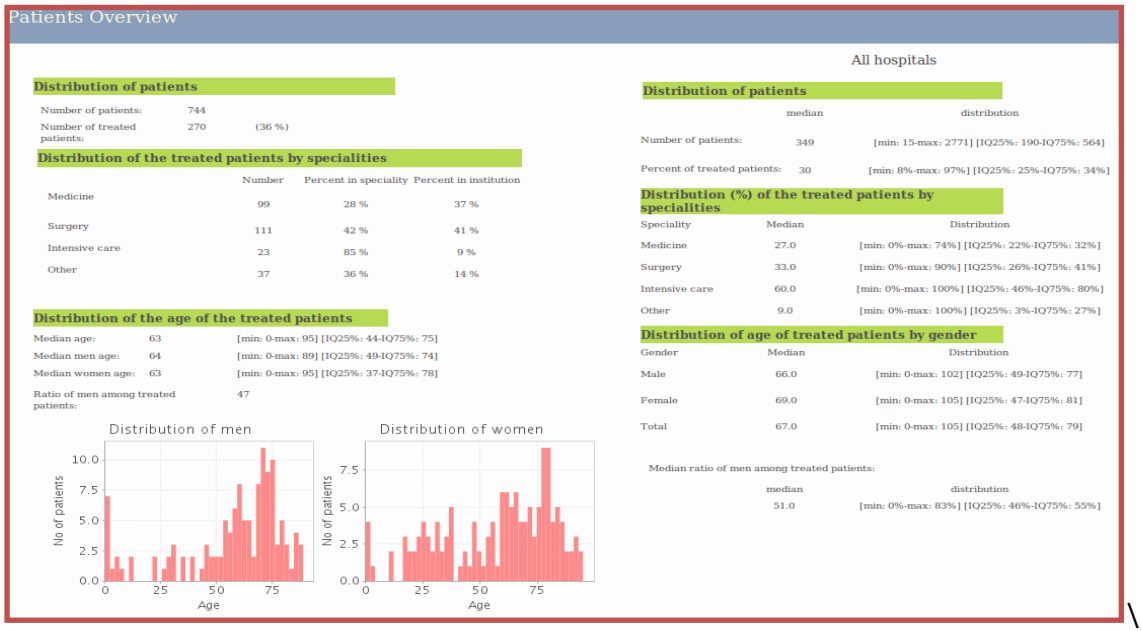


Figure 6.8 ESAC WebPPS data output for hospital point-prevalence surveys



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7. Effective risk communication in promotion of integrated surveillance for antimicrobial resistance

Figure 7.1 Risk analysis framework

7.1. Background and rationale

Antimicrobial resistance requires a comprehensive and collaborative risk management response. The risk analysis framework, promoted by WHO and the Food and Agriculture Organization of the United Nations (FAO) to address hazards in the food supply, comprises three essential components: risk assessment, risk management and risk communication (Figure 7.1). Risk communication is broadly defined as the interactive exchange of information and opinions concerning hazards and risk management options among assessors, managers, consumers and other interested parties about threats to health, safety or the environment. The purpose of risk communication is to increase knowledge about the nature and effects of risk, in order to promote collaborative work in the search for solutions.

The emergence of antimicrobial resistance in disease-causing bacteria is a public health concern that poses unique communication challenges. Antimicrobials are essential for treating infectious disease

in both humans and animals. However, their use may lead to the emergence of new strains of bacteria that cannot be treated with commonly used antimicrobials. Sometimes, pathogens emerge that are resistant to multiple antimicrobials, making treatment extremely difficult. A further complication is the fact that antimicrobials are commonly used in food animals, such as cattle, swine, and poultry, which are a common source of exposure to human pathogens linked to food.

This section focuses on crafting an effective communication strategy to support the work of AGISAR and national governments in controlling antimicrobial resistance.

Risk communication can be divided into three general categories: core communication, consensus communication and crisis communication.

- Core communication is the sharing of information on health risks that have been identified through scientific research and are non-controversial.
- Consensus communication aims to bring about consensus on how controversial risks should be managed.
- Crisis communication focuses on communication in situations where sudden adverse events may pose a risk to public health.

In any risk communication, consideration of the audience and active listening to their opinions, views and concerns are essential.

Risk communication uses specific tools and strategies to provide appropriate information without triggering an over-reaction. Effective communication empowers the listener: it provides specific and timely information and advice on how to reduce or control risks. Effective core communication is the result of careful planning, together with a strong scientific understanding of the hazards and their public health impact.

Integrated surveillance activities and collection of data on antimicrobial resistance will generate information of interest to multiple stakeholders, including government risk managers, farmers, food manufacturers, retailers and consumers. For example, food producers may be concerned about the public disclosure of information on their production practices, including the use of antimicrobials in animal husbandry, while consumers may be concerned that food is contaminated by resistant pathogens. Risk managers must be prepared to address the concerns of stakeholders at any point during the surveillance process.

Effective risk communication is critical to successful adoption of integrated surveillance programmes for antimicrobial resistance. In this section, the lessons learned on risk communication from two

AGISAR pilot studies, in Kenya and Ecuador, will be examined and recommendations extracted for project planners.

Box 7.1 Objectives of risk communication

- Identify the public perception of risk and health concerns related to antimicrobial resistance.
- Promote increased understanding of the objectives and potential risks of antimicrobial use.
- Increase awareness about non-pharmaceutical actions to reduce the risk of antimicrobial resistance.
- Educate food producers about the health consequences of the misuse or abuse of antimicrobials in food production and about the importance of implementing good practices to reduce the risk of antimicrobial resistance.
- Use the media and social networks to spread information on the health consequences of the misuse or abuse of antimicrobials in food production and on good practices in food production.
- Create culturally appropriate communication channels to provide information based on scientific evidence, and to allow people to express their concerns, opinions and proposals on reducing the risk of antimicrobial resistance.

Box 7.2 Objectives of social mobilization

- Raise awareness of partners, allies and stakeholders regarding the importance and objectives of integrated surveillance, and involve them in project implementation (including informing them promptly on progress, challenges and results).
- Include national, regional and local authorities in the formulation and implementation of the project, with clearly defined areas of responsibility, and secure the support of authorities for specific tasks, such as staffing, resource allocation, and public appearances.
- Identify lessons learned and communicate them to policy-makers and stakeholders involved in the formulation and implementation of the project.

7.2 Goals and objectives

Communications activity is not an end in itself but should serve, and be aligned with, the strategy and objectives of the overall programme. From the very beginning, the objectives of communication should be clearly defined and an appropriate strategy devised.

Clear communication is essential if scientific information on antimicrobial resistance is to be shared effectively. To be relevant and understandable, communication needs to take into account the intended audience, so it is important to identify and understand the audience in advance. For the general public, well targeted messages using non-technical language are most effective; consumers are especially interested in specific information on the nature, form, severity, or magnitude of the risk, together with steps they can take to avoid or minimize the effects of exposure.

The communication strategy should be a dynamic and integrated effort that includes identifying collaborators (partners and allies), building capacity, establishing surveillance and monitoring mechanisms, listening to the public, and disseminating effective key messages. A well-conceived strategy can support both the development of the programme and the dissemination of results.

When an integrated surveillance system is being established, effective communication can motivate a variety of stakeholders, including governments, producers, and researchers, to participate. Strategies for engaging stakeholders and building consensus should consider both the timing and the content of the communication. As the findings from surveillance activities become available, communication can help engage stakeholders in a discussion of risk management. It is vital that the communication strategy anticipates concerns that might be raised at any point by different stakeholder groups.

The pilot studies in Ecuador and Kenya showed that, when stakeholders were consulted about the objectives and design of the surveillance activities and had input into data collection, they became more engaged in the project. Close interaction will also ensure that the data requirements of the intended users, in terms of quality, access, relevance, etc., are better understood and addressed. Through continuous interaction between data providers and data users, projects can have a greater impact.

It is therefore important that integrated surveillance programmes consider the following activities as part of their communication plan:

- Involve stakeholders from the very beginning of the project, informing them about the project objectives and anticipated results.
- Ensure continuous long-term interaction with key players along the farm-to-table continuum.

Build a platform for systematic communication with stakeholders, including sharing interim data and final results, raising awareness about antimicrobial resistance, and capacity-building among primary stakeholders for monitoring and control of antimicrobial resistance.

Box 7.3 Risk communication plan

- Assess communications capacity and leadership, both among the project staff and externally.
- Identify stakeholders (including media, government departments, veterinarians, farmers, food processing industry, pharmaceutical industry, wholesale and retail food distributors and the general public) and establish the key concerns of each stakeholder group through dialogue.
- Together with the stakeholders, identify the target audiences for risk communication on antimicrobial resistance; establish participatory mechanisms to obtain input from the target audiences on their perception of the risks (including concerns, fears and worries), and tailor messages accordingly.
- Analyse the specific concerns to identify recurring themes and general concepts to be addressed.
- Develop key messages for each concern (both general and specific) of the stakeholders.
- For each message, identify key facts and information to support it.
- Test messages with the target audiences to whom they are directed.
- Plan for the broadcast of messages (including identifying suitable dissemination channels for the target audiences).

7.3 Define key stakeholders and target audiences

The pilot studies in Kenya and Ecuador showed that it is indispensable to undertake a thorough stakeholder analysis with regard to antimicrobial resistance. Both studies clearly highlighted that the positions and interests of the various stakeholders influence the choice of strategies for ensuring their involvement.

A stakeholder is a person or group that has something to gain or lose through the outcomes of a process or project. In many circles, stakeholders are called interest groups, and they can have a powerful bearing on the outcome of a political process. It is beneficial to identify and analyse the needs and concerns of different stakeholders, particularly when their support may be useful in influencing policy relating to antimicrobial resistance.

In efforts to link research to policy, stakeholder analysis is used to identify the parties engaged in conducting the research, those who make or implement policy, and the intermediaries between them. Stakeholder analysis helps define the audience for the research, what their positions and interests are, and the best approach for presenting research results. Identifying methods for early stakeholder engagement can help ensure that the research approach is understood and accepted. In this way, stakeholders can be engaged around a policy issue or debate in a manner that can influence the outcome.

The key stakeholders for integrated surveillance of antimicrobial resistance include government risk managers, food producers, other food industry, retailers and consumers. In some countries, the drug industry may also be a stakeholder.

In the countries where pilot studies were conducted, government officials, producers, and retailers were all highly motivated to participate in the surveillance project. In the Ecuadorian pilot study, for example, researchers found that both the government and the industry believed that the surveillance programme would make them more competitive for trade in the region. No one expressed concerns about an adverse impact on the domestic market.

Poultry farmers participated actively, with the understanding that the pilot study would inform them about the risk factors associated with both the prevalence of *Salmonella* in their flocks and the antimicrobial resistance profile of the *Salmonella*. Farmers were also informed that, following the pilot study, they would be given help to develop more effective methods to control *Salmonella*.

Researchers found that food producers wanted to know about the health of their flocks in order to improve their market competitiveness. Producers should be engaged early in any pilot study, to ensure that they are informed and do not react negatively as the study progresses.

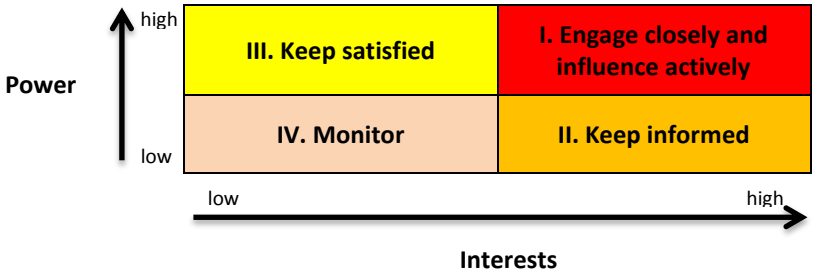
Identifying and addressing the key areas of concern for consumers and retailers should also be considered early. Their support can be vital to successful implementation and they will have a strong interest in the results of the surveillance. Retailers can also serve as a sample collection point.

Once stakeholders have been identified, they can be grouped as "primary" or "secondary". Primary stakeholders are those, like producers, whose daily activities have a direct impact on the study and for whom the surveillance activity might affect those activities, either positively or negatively. Secondary stakeholders include the retailers and consumers who sell and purchase products. While the surveillance activities may have a less direct impact on these stakeholders, they may nevertheless have a strong interest in the research and its results.

Figure 7.2 shows a grid that can be used to classify stakeholders according to their interest and power.

- Interest reflects the degree to which stakeholders are likely to be affected by the integrated surveillance activities and the degree of interest or concern they express about antimicrobial resistance.
- Power indicates the influence stakeholders have over the project, and the degree to which they can help achieve, or block, the desired change.

Figure 7.2 Stakeholder analysis



Source: adapted from ref. 1

Stakeholders vary by country or region, so it is important to assess where these groups or individuals sit on the “interests” and “power” paradigm. The goal of this exercise is to identify and engage fully those stakeholders with high power (both individuals and organizations), especially if their interests align with the integrated surveillance. In most countries, the decision-makers, usually members of the government, will sit at the very top of the power scale. Beneath these are people whose opinion

matters – the opinion leaders. Stakeholders with high interest but low power need to be kept informed; if well organized, they may form the basis of an interest group or coalition that can advocate for policy change. Those with high power but low interest should be engaged as they may be helpful as patrons or supporters of the proposed policy change.

The Kenyan pilot study identified the following strategy for stakeholder communication as highly successful:

(a) continuous interaction and communication of key data and findings with the primary stakeholders;

(b) regular involvement of secondary stakeholders, including policy-makers, at the beginning of the project, followed by increased involvement during the interim and final dissemination workshops.

7.4 Elaborate the key messages

- The initial step in the development of message is to know the audience, their social, cultural and economic experiences and their pre-existing knowledge on the subject. The participation of an interdisciplinary team can be helpful in assessing the concerns and priorities of the different stakeholder groups. In designing the key messages, it is important to evaluate the following questions: To what extent can the risks be controlled by consumers or producers?
- Are actions in one part of the food chain increasing the risk in other parts?
- Are the benefits of a particular technology shared equally? Do the risks of a technology fall disproportionately on one part of the food chain?
- Are alternative production methods available?
- What background information will be needed to give advice to the public and other stakeholders during a food crisis?

Antimicrobial resistance incorporates many of these issues, as the risks to consumers may arise from the actions of producers much earlier in the food chain. In other words, antimicrobial use in animal production may benefit producers while increasing the risk to consumers.

While the relative emphasis on either commercial or public health messages can be different for different stakeholders, all communication messages should be consistent and aligned, so that they work effectively together. It may well happen that communication on antimicrobial resistance surveillance programmes takes place with all stakeholders in the same venue, and it is important to be consistent in order to establish and maintain trust.

A number of important steps need to be taken in planning for the release of the results of surveillance. National risk managers should anticipate possible scenarios and stakeholder responses, so that they have time to consider communication options and opportunities. During the dissemination phase, planners should also identify likely risk management options and prepare for discussions with stakeholders.

While information on antimicrobial resistance can be important for international health assessments, the primary objective of the pilot study is to provide useful information for policy planning in the country. In developing a common platform for collection of information from country surveillance programmes, planners should work with risk managers in the countries to determine their information needs.

Each country and region will have to determine appropriate strategies and key messages. However, the AGISAR pilot studies illustrated several approaches.

- In the Kenya study, researchers found that information on the antimicrobial resistance profile of bacteria in meat was most relevant for engaging stakeholders. Producers were concerned about the impact that resistant pathogens might have on consumers. While producers generally considered that they were using minimal amounts of antimicrobials, as animals were pasture-reared, surveillance information was needed to support or disprove this belief.
- In the Ecuador study, researchers found that a key motivation was to improve the trade position with regional partners. Producers and the agriculture sector in general wanted to increase the competiveness of the industry and access to export markets. The health sector was responsive to the effort to reduce the level of antimicrobial resistance in human and veterinary medicine. Retailers wanted to increase consumer confidence, and consumers wanted to buy safer products.

When preparing messages, it should be remembered that data need to be made “usable” for the policy-making and risk management communities, i.e. information needs to be conveyed in a language that is understandable and user-friendly, without distorting or misrepresenting the data.

7.5 Define the implementation strategy

The implementation strategy is developed through an iterative process that feeds into the development of the risk communication plan, and will necessarily evolve over time. Preliminary research and context analysis should identify the stakeholders and develop effective messages. A

plan for implementation and leadership should be drawn up. Finally, continuous evaluation is important to allow timely improvements to be made to the strategy. The timing of communication is an important consideration, as each stage of the programme will have different objectives.

- **Developing support for the programme and educating groups.** In the early stages, a major task of risk communication is to encourage support for and participation in the programme, and to identify and educate groups of stakeholders.
- **Ensure smooth operation.** Once the programme is running, it is especially important to keep open communications with the primary stakeholders and participants, those involved in the day-to-day operations. This includes regularly asking about problems or concerns and responding to them in a timely way.
- **Keep communication channels open.** While data are being analysed, it is important to keep communications open, and to help stakeholders understand the process and the timeline for dissemination of results.
- **Keep all stakeholder groups informed about results.** It is important that information is released to all stakeholder groups, with consideration given to the issues of concern to each. Ideally, this should be done in a meeting, allowing all stakeholder groups to hear, question and respond to the information at the same time. This provides the best opportunity for stakeholder groups to assess the importance of information, as they can also hear other stakeholders' questions and comments. An open forum can also provide an opportunity for balanced media coverage, as different views are likely to be expressed.
- **Continuously review and evaluate communications materials and approaches.** The effectiveness of the communications strategy should be regularly reviewed, and changes made to materials, spokespersons, or outreach methods as necessary.
- **Prepare for adverse events.** The team should make advance preparations to respond rapidly to any adverse events reported in the media.

7.6 Evaluate the risk communication messages

Evaluation is essential for improving risk communication and risk management, and should be an ongoing process. The components of evaluation include the following.

- **Evaluation of learning**: how can uptake of information be increased?
- **Evaluation of the process:** what are the mechanisms for engaging with stakeholders and how can they be improved?
- **Evaluation of the product:** how are the disseminated data being used?

- **Evaluation of the outcome:** which communication strategies have worked well to increase data use?

Information from the evaluation should be shared among programme managers and senior members of the communications team, and used to make improvements to the risk communications plan, capture lessons learned and formulate recommendations for the future.

7.7 Other important considerations

The communication strategy should allow stakeholders to air their concerns in an environment where they can be fully discussed by all interested parties. This helps avoid problems that may occur when one or more stakeholders is not involved in the discussion. In such a case, the media may be used to air issues that can be more easily resolved within a well managed dialogue among the stakeholders.

Media communications should not be used as a substitute for effective communication with stakeholders. However, sometimes the media can be a critical component in disseminating information, especially during an emergency.

The communication strategy should educate consumers about the hazards of antimicrobial resistance and the potential pathways of exposure to pathogens, through both food and the environment. The media can be instrumental in reaching large numbers of consumers, and provide a ready-made platform for outreach and education campaigns.

Issues that arise during an emergency can be exceptional, and it is important to develop crisis communication strategies in advance. While the purpose of the risk analysis framework is to avoid food safety emergencies, it is indeed the case that much risk communication takes place during emergencies. During a food safety emergency, it is essential to provide the necessary and appropriate information to consumers as simply and clearly as possible. Describing the specific steps that consumers can take to minimize their own risk will help the public respond to the food safety hazard appropriately, and reduce the likelihood of misinformation, which can lead to the public avoiding certain food products long after the emergency is over.

During a food safety emergency, coordination between communication bodies in the public and private sectors is vital, and should include consumer organizations. Health and agriculture agencies should liaise with other lead communicators to ensure consistent messages. Countries should develop and agree upon emergency communication plans and ways to deliver public health messages through the local and national media. Sharing the successes and failures of risk

communication during previous food safety events can help to improve future strategies for alerting and educating the public on how they can best protect themselves and their families.

Risk communication plans should also be part of a rapid alert system. Many countries and regions use these systems to notify governments and industry about contaminated products in the market, so that they can be removed. Risk communication should also be directed to retailers and consumers.

7.8 Examples of successful risk communication

7.8.1 Containment of fluoroquinolone resistance in Australia

In Australia, fluoroquinolone resistance was controlled through effective expert communication approaches, which led to regulatory controls at the national level. National guidelines for antimicrobial drug use have been in effect since 1976. They are reviewed and updated every three years by a panel of infectious disease experts. The use of quinolones in human medicine has been actively contained under these guidelines, which recognize their status as a reserve category of medicine, to be used for a limited number of indications and for acute cases requiring hospitalization.

The Australian Expert Advisory Group on Antimicrobial Resistance also advised that quinolones should never be used in food-producing animals because of the risk of drug resistance developing in enteric pathogens and their potential transmission to humans through the food chain. Australia has therefore not approved quinolone use in this sector, unlike other countries, where the drugs are often added to drinking-water for poultry and are used in cattle.

This policy has effectively controlled quinolone resistance in Australia. Human cases of quinolone-resistant *E. coli* infection in Australia rose from 1% in 1998 to 5% in 2010, while rates in the USA increased from 3% to 17% between 2000 and 2010. In Europe, as many as 45% of isolates were resistant in 2008.

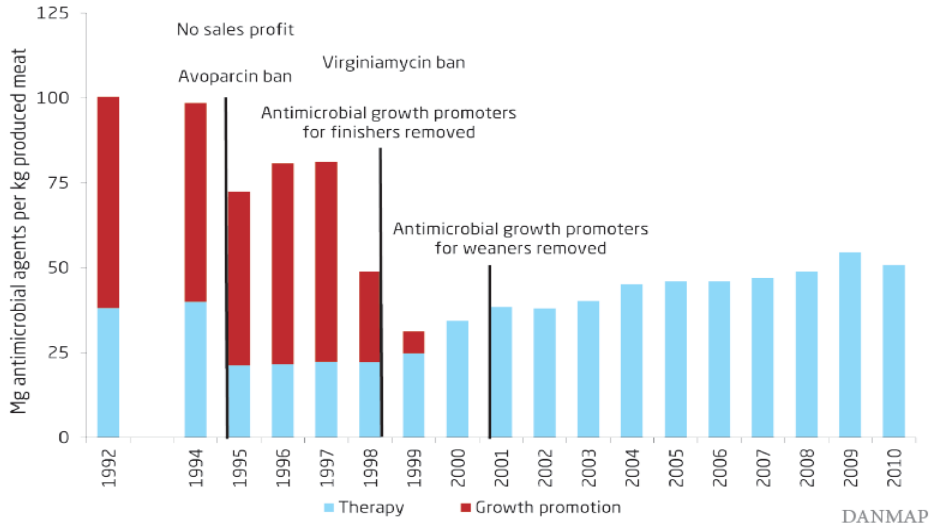
7.8.2 Restriction of antimicrobial use in animals in Denmark

Since the mid-90s, Denmark has cut by 60% the use of antimicrobial agents per kilogram of livestock produced. In the same time period, the country's pork production has increased by 50%. Denmark is the world's largest exporter of pork, exporting 90% of the pork it produces. Some reasons for the success in Denmark include a widespread public awareness of the problems caused by the overuse of antimicrobials, development of a comprehensive surveillance system to track and target overuse, and laws prohibiting veterinarians from profiting from the sale of drugs to farmers. The Danish antimicrobial surveillance programme, DANMAP, issued a pamphlet (“Data for action”;

www.danmap.org) to raise awareness in the international scientific community and among policy-makers of the need to collect data to assess the status of antimicrobial consumption, its impact on antimicrobial resistance, and the effectiveness of interventions.

Since 1995, Danish legislation has permitted antimicrobial treatment of animals only if they are diseased or have a well established infection. Prophylactic use of antimicrobials is illegal. The figure below, taken from the Danish pamphlet, indicates the fall in antimicrobial consumption in pigs following this ban and other interventions.

Figure 7.3. Change in antimicrobial use in pigs in Denmark, 1992-2010



Source: *Data for action;* www.danmap.org

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Annex 2. Examples of programmes on surveillance of antimicrobial resistance in animals, food and humans

Australia

Department of Agriculture, Fisheries and Forestry(DAFF). Pilot surveillance programme - animal (http://www.daff.gov.au/agriculture-food/food/regulation-safety/antimicrobial-resistance/antimicrobial_resistance_in_bacteria_of_animal_origin)

Canada

Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). Human, animal, food (http://www.phac-aspc.gc.ca/cipars-picra/index-eng.php)

Denmark

Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). Human, animal, food (http://www.danmap.org)

Europe

European Antimicrobial Resistance Surveillance Network (EARSS). Human (http://www.rivm.nl/earss/)

European Surveillance of Antimicrobial Consumption (ESAC). Human usage (http://app.esac.ua.ac.be/public/)

European Food Safety Authority. Animal, food, human (http://www.efsa.europa.eu/)

Finland

Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of Antimicrobial Agents (FINRES-VET). Animal, food (http://www.evira.fi/portal/en/about+evira/publications?a=view&productId=238)

France

Observatoire national de l'Épidémiologie de la Résistance bactérienne aux Antibiotiques (ONERBA). Animal, human (http://www.onerba.org/)

Italy

Italian Veterinary Antimicrobial Resistance Monitoring (ITAVARM). Animal, human (http://195.45.99.82:800/pdf/itavarm.pdf)

Japan

Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM). Animal (http://www.maff.go.jp/nval/tyosa_kenkyu/taiseiki/monitor/e_index.html)

Netherlands

MARAN. Animal, food (http://www.wageningenur.nl/en/Research-Results/Projects-and-programmes/MARAN-Antibiotic-usage.htm)

Norway

Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway (NORM-NORMVET). Human, animal, food (http://www.vetinst.no/eng/Research/Publications/Norm-Norm-Vet-Report)

Sweden

Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM). Animal (http://www.sva.se/en/Antibiotika/SVARM-reports/)

United States of America

National Antimicrobial Resistance Monitoring System Animal Isolates (NARMS). Human, animal, food (http://www.ars.usda.gov/Main/docs.htm?docid=6750&page=1)

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