Surveillance standards for antimicrobial resistance

World Health Organization

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Introduction

The continuing emergence of pathogenic micro-organisms that are resistant to first-line anti-microbials is a cause of increasing concern. This emergence is associated with higher levels of mortality and morbidity which not only impacts on patients but also increases the burden on health care services as a result of additional diagnostic testing, prolonged hospital stay and increased intensity and duration of treatment.

Although the mechanisms by which organisms acquire resistance are often well understood, including the selective pressures arising from exposure to antimicrobials, the precise role of drug usage in selection of drug resistance has yet to be fully elucidated. Nonetheless, there is evidence to suggest that more prudent usage of antimicrobials particularly in the treatment of human disease, but also in veterinary practice, animal husbandry and agriculture, could make a significant impact on the pace and extent to which resistance emerges in microorganisms pathogenic to man.

To be effective, the control and prevention of infection due to resistant microorganisms must be an integral part of the prevention and management of communicable diseases in general. Thus, describing the distribution of infection due to resistant organisms within populations, together with changes in patterns of those infections over time, provides the basic information for action both to control disease caused by resistant microorganisms and to contain the emergence of resistance. Used in conjunction with disease prevention and infection control procedures and data on antibiotic usage, strategies can be developed to protect the public health now and in the future.

The purpose of this manual

The purpose of this manual is to provide national agencies with a framework within which existing surveillance of communicable disease and infection can be reviewed in order to determine the priorities for epidemiological surveillance of diseases caused by microorganisms exhibiting antimicrobial resistance. The manner of implementation of antimicrobial resistance surveillance most appropriate in a particular country will be determined by a number of factors, including the range of diseases of public health significance, the organization of healthcare services and the resources available. Although a national implementation plan involves a national reference laboratory in collaboration with epidemiological expertise, many of the recommendations can be implemented by local clinical microbiology laboratories. Hence these guidelines can be useful for professionals in a number of positions in the health care system including medical officers in the ministry of health, public health microbiologists and epidemiologists and clinical microbiologists.

This manual is confined to surveillance of resistance in bacterial infections other than tuberculosis. For surveillance of drug resistance in tuberculosis and malaria, reference should be made to *Guidelines for Surveillance of Drug Resistance in Tuberculosis* (*1*) and *Assessment of Therapeutic Efficacy of Antimalarial Drugs* (*2*), respectively.

This manual is designed to be used in conjunction with the *WHO Global Strategy for Containment of Antimicrobial Resistance* (*3*), *WHO Recommended Surveillance Standards* (*4*) and the *WHO Protocol for the Assessment of National Communicable Disease Surveillance and Response Systems* (*5*).

Surveillance of communicable diseases

Overview

Those with responsibility for ensuring that health care services operate optimally need information on the distribution of disease and its determinants so that provision of services can be appropriate. Surveillance is a tool that can facilitate the prevention of infection and the amelioration of its immediate and long-term effects by providing the necessary information for action. In the document *WHO Recommended Surveillance Standards* (*4*), a method for the development of a national plan for communicable disease surveillance is proposed and the clinical and laboratory data required are identified. These are summarized below.

Clinical data

Surveillance of communicable disease and infection involves the collection of data relating to clinically-observed illnesses in individuals. The strength of surveillance systems, where the primary route of reporting is from clinicians caring for individual cases, is the capacity to provide timely information on clinical disease. To maximize the timeliness of surveillance, clinical reporting is frequently initiated by the suspicion of the disease or syndrome. However, reporting of data that become available later, including laboratory confirmation of the diagnosis and antimicrobial susceptibility, may not be undertaken, may often be delayed, or may fail to confirm the originally suspected diagnosis.

Furthermore, data obtained from clinical sources is generally unrepresentative of the totality of disease within a population. The reasons for this are diverse. It is well recognized that not all individuals suffering from infections seek help. Whilst this may be most marked in trivial and self-limiting illnesses, it is also true of potentially life-threatening conditions. The accessibility and cost of treatment together with cultural and behavioural factors are powerful determinants as to whether individuals seek help for their condition. In addition, the completeness and quality of the data from clinically-based surveillance systems depends on accuracy and consistency in diagnosis, assiduous record-keeping and reporting that is timely, accurate and complete.

Laboratory data

The strength of laboratory information is that it provides objective confirmation of the diagnosis. The investigation of appropriate biological samples not only allows confirmation of the clinical diagnosis, but also provides the opportunity for more detailed characterization of the causative organism. Such characterization, through speciation, grouping and typing (including molecular typing) assists in the more precise analysis of clusters of disease. Information on antimicrobial susceptibility is frequently of value in determining the most appropriate treatment for both individuals and groups who have a particular clinical syndrome. However, information obtained from the laboratory is necessarily less timely and frequently contains only scant clinical details.

In most instances, laboratory data will be available only where patients have sought medical assistance and the relevant tests have been instigated to assist in the diagnosis and treatment of the patient. As a result, in the absence of specific arrangements, laboratory data will normally be available only where such tests add to the diagnosis and management of the patient. The quality and completeness of laboratory data will depend on consistent technical standards together with assiduous record-keeping and reporting that is timely, accurate and complete.

Surveillance of antimicrobial resistance

Ideally, surveillance of antimicrobial resistance should involve the collection and collation of both clinical and microbiological data. By establishing surveillance systems that integrate clinical and laboratory data, not only can the necessary data be captured but the strengths of both data sets can be combined.

There is evidence that the wiser use of anti-
microbials may diminish the rate at which resist-
ance emerges. Thus information from surveillance
of antimicrobial resistance in conjunction with data
on the use of antimicrobials provides a powerful
tool for the containment of resistance.

Surveillance of antimicrobial resistance

Objective

The objective of surveillance of antimirobial resistance is to provide the information necessary to secure an approach to the management of communicable diseases that minimizes morbidity and mortality whilst also containing the emergence of pathogens resistant to antimicrobials. The principal uses of the information gained from surveillance are to optimize the use of antimicrobials and assist in the prevention, control and containment of antimicrobial resistance at the local, regional and national levels by:

- defining/updating guidelines for empirical (syndromic) treatment and standard treatment guidelines

- reassessing the national formulary

- assuring that drug supplies are appropriate for needs

- identifying need for implementation of infection control measures

- monitoring the impact of interventions to improve antimicrobial use and control the spread of infection.

General principles

Systems to describe the patterns of communicable disease together with the resistance of their causative organisms are increasingly important components of local, intermediate, national and international surveillance. To be effective such systems should:

- be focused on those diseases of greatest public health importance (i.e. with high mortality and/or morbidity, and where therapeutic options may be severely limited by antimicrobial resistance)

- include diseases that are readily transmissible (i.e. may give rise to outbreaks and epidemics)

- provide information on mortality and morbidity attributable to resistant strains of the organism in the context of that attributable to susceptible strains (i.e. be integrated with communicable disease surveillance systems)

- provide information for action at the local, intermediate and national levels.

To be successful, participation at the local level should be made as easy as possible. Thus systems should capture the minimum amount of data needed for useful surveillance and an evidence-based approach to public health interventions, and ensure that the technical requirements to generate, collect and collate these data at the local level are as simple as possible and performed according to a prescribed timetable.

To provide reliable information for action:

- Data on antimicrobial resistance should be of a consistently appropriate quality i.e. use methodologies that achieve or exceed the standards set out in *Basic laboratory procedures in clinical bacteriology* (6)

- The capture, collation and analysis of data should be in accordance with protocols of appropriate quality i.e. achieve or exceed the standards set out in *WHO Recommended Surveillance Standards* (4)

- Information outputs should facilitate decision-making by clear presentation and timely distribution, and should include a commentary on the limitations of the data presented as well as proposals for interventions.

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

Resistance to antimicrobials can be categorized as:

- *Prevalent*: Resistance to a particular antimicrobial agent in clinical use that occurs to a lesser or greater extent in part or all of a country and has an impact on patients and/or the provision of health care.

- *Potential threat*: Resistance to a particular antimicrobial agent in clinical use that occurs elsewhere in the world and is having an impact on patients and/or the provision of health care, with the possibility of arising within, or spreading to, the country under consideration.

- *Theoretical threat*: Not a prevalent problem nor a potential threat, but an organism having the theoretical risk of exhibiting resistance which would have a significant impact on the management of individual patients and/or public health.

- *Unknown*: In many countries the prevalence of antimicrobial resistance is unknown particularly among pathogens causing infections in the community.

Determining the priority diseases for surveillance of antimicrobial resistance

Priorities for surveillance should be developed in the light of the pattern of disease, the existing infrastructure and the resources in each country. The priority diseases for surveillance of antimicrobial resistance should be part of the overall priorities for surveillance in the individual country. However, due consideration should also be given to emerging problems in adjacent countries and internationally.

Gap analysis

The development of systems for the surveillance of disease due to microorganisms resistant to antimicrobials should be undertaken in the context of current surveillance systems. Some diseases in which resistance is an existing or potential problem may already be the subject of surveillance. Therefore, an analysis of existing surveillance systems for priority diseases should be undertaken and in the light of that analysis, the developments necessary to meet the antimicrobial resistance surveillance needs of the country, locality or institution should be identified. For this purpose *Protocol for the Assessment of*

National Communicable Disease Surveillance and Response Systems (5) provides useful guidance.

Available resources

Resources for microbiological testing and surveillance will always be finite. Choices need to be based on national priorities. This manual is set out to assist in the identification of the most appropriate surveillance method for a particular disease or microorganism and contains protocols for surveillance of the major bacterial infections/pathogens.

Epidemiological methods

The most appropriate approach to the surveillance of each infection and the resistance of the causative organisms needs to be determined in the light of the information required and the ability to collect the relevant data. The capacity to undertake surveillance varies depending on the type of infection and the health system setting.

Population

Infections are frequently characterized by the setting in which they are acquired i.e. community or health-care-facility-associated (nosocomial). The microbial species causing community-acquired and hospital-acquired infections, as well as their antimicrobial resistance patterns, tend to differ. However, these settings are neither completely discrete nor separate. Patients with community-acquired infections may be treated in healthcare facilities and infections acquired in hospital may not manifest themselves until the patient has returned home. Patients who are re-admitted after a short period at home might be infected with a bacterial strain originating from the hospital environment. Consequently, surveillance of antimicrobial resistance should not only describe infection in terms of the setting in which it is acquired but also in relation to the population as a whole.

Types of surveillance

Two general approaches to surveillance may be considered:

- *Comprehensive surveillance*: The surveillance of a specified disease (or pathogen) in the whole population at risk involves the capture of data on all cases of infection. Since this requires the involvement of a wide range of cli-

nicians and laboratories, it is normally suitable only for the collection of limited sets of data e.g. date of birth, gender, location, type of specimen and resistance pattern.

- *Sentinel surveillance*: The collection of data from a limited catchment area or population to serve as indicator data for the rest of the population is generally more suitable where prolonged, ongoing and detailed data collection is required. Normally the sentinel population should be representative of the total population but in certain circumstances, where the primary objective is to detect the emergence of resistance, a targeted approach may be more appropriate.

The ability to obtain appropriate specimens from the whole or a representative sample of the population under surveillance will vary between countries and settings and in some settings and for some infections, it may not be practicable to undertake comprehensive surveillance. In these instances, it may be more appropriate to take a sentinel surveillance approach, whereby limited but reliable data can be generated if there is proper sample definition and consistency between the participating sentinel sites. However, the surveillance capacity in a country may be greater than first realized if existing resources are reviewed and optimized.

Whether surveillance should be **continuous** or **episodic** (i.e. undertaken over limited periods of time) needs to be determined in the light of the resources available. Episodic surveillance may be suitable in resource-limited situations or for diseases that are predictably seasonal. In these circumstances, surveillance can be developed with the possibility of extending the time period, should that be required.

Irrespective of whether surveillance is continuous or episodic, surveillance may be defined as:

- *Passive*: Where reports are awaited and no attempt is made to seek reports actively from the primary data collector in the surveillance system; or

- *Active*: Where reports are sought from the primary data collector in the surveillance system on a regular basis.

As part of either of these approaches surveillance may be:

- *Routine*: The regular systematic collection of a specified data set; or

- *Enhanced*: The collection of additional data about cases reported under routine surveillance, under predetermined and specified circumstances.

Representativeness

The presentation of patients to health care services and their subsequent investigation is neither uniform nor consistent. Therefore, it is important to understand the relationship of the population surveyed to the wider population. This is particularly important in relation to non-random sentinel surveillance. It may be appropriate to undertake cross-sectional studies periodically to establish the extent to which data from sentinel sources reflect the wider community.

Numerators for surveillance

For reliable information, data should relate to a single episode of illness in a patient. For microbiological data, only the first positive culture from the patient for each disease episode should be reported for surveillance purposes, even if several positive cultures are obtained, or resistance emerges during treatment.

Denominators for surveillance

Wherever possible, rates should be expressed in terms of cases within a defined human population in a defined time period. Since the submission of microbiological specimens for analysis is inconsistent and varies widely, **the use of laboratory specimens and isolates as denominators produces rates that are of limited epidemiological relevance unless linked to disease incidence**.

Trigger events

The capacity to undertake surveillance will always be finite and therefore it may be necessary to have contingency plans to initiate surveillance or other investigative approaches. Where events are infrequent, cross-sectional studies may provide the information required. To ensure outbreaks are recognized in a timely way, it is crucial to ensure that triggering mechanisms (e.g. reporting of unusual or untoward events, including the emergence of resistance) have been determined and are in place.

Maintaining surveillance standards

The implementation of an integrated national surveillance system is facilitated if it is coordinated centrally by a single agency. There are also advantages in the use of standardized technical systems, reporting methods and audit processes. Such approaches will promote consistency throughout the system. In order to ensure that the surveillance methods result in accurate and timely outputs, they should also be subject to regular audit.

Microbiological methods

Surveillance of infections due to resistant organisms is dependent on all of the following:

- Obtaining appropriate specimens from the infected individual

- Successful isolation of the causative organisms

- Accurate determination of antimicrobial resistance

- Data collection, collation and analysis

- Dissemination of appropriate information for action.

Specimens for laboratory testing

The collection and processing of specimens for surveillance purposes should be undertaken in a consistent way and to the appropriate quality standard. Wherever possible, the procedure for obtaining specimens should be readily understood and acceptable to the patient (simple, quick and, where possible, non-invasive) and should minimize the risk of false negative and false positive results, particularly from contamination by commensal or other organisms.

Tests on specimens obtained from normally sterile sites, which may involve invasive procedures (e.g. blood, CSF), normally have a higher positive predictive value for infection than those from other sites (e.g. throat swab, sputum and skin).

Arrangements for microbiological testing

Common infections caused by bacteria that are readily isolated and require little detailed characterization are more likely to be reliably and consistently identified than those due to organisms that are uncommon, difficult to culture, slow-growing, or requiring complex procedures for their characterization. Thus, in considering what is most

appropriate, authorities need to consider whether isolation and/or testing should be undertaken in local (general) microbiology laboratories or specialist reference laboratories. Where reference laboratories undertaking detailed characterization of the microorganisms exist, there will normally be advantage in assigning the task of susceptibility testing to those laboratories.

Where it is determined that it is more appropriate to undertake testing in laboratories distant from the health care setting, it is necessary to ensure that:

- the specimen is suitable to transport

- the transport methods are safe, in compliance with transport regulations and ensure that the specimen arrives at the testing laboratory in optimal condition (*7*)

- arrangements are in place to ensure the timely flow of information for both clinical and surveillance purposes.

Maintaining microbiological standards

In order to ensure that the microbiological methods are of a consistently appropriate standard, laboratories engaged in surveillance should be participants in quality assurance programmes.

Microbiological representativeness

In order that microbiological testing produces consistent and reliable information:

- Specimens for testing should be selected to optimize the identification of the presence of disease in the individual and should preferably be collected before antimicrobial treatment is initiated

- Colonies selected for susceptibility testing should be representative of the culture as a whole and the results of susceptibility testing *in vitro* should be known to correlate with the likely clinical effect of the antimicrobial.

It may be neither possible nor appropriate for all organisms warranting some level of monitoring to be incorporated into routine surveillance systems. A spectrum of approach can be used from:

- susceptibility testing of all isolates of the organism from the appropriate specimens in the local laboratory, as part of a comprehensive surveillance system, to

- the submission of selected specimens (e.g.

from patients in whom treatment has failed, for various reasons) to obtain indicative data on susceptibility, as part of a non-random sentinel surveillance system.

The former arrangement is more suited to surveillance of prevalent resistance whilst the latter is more suited to monitoring potential or theoretical threats.

In a few specific cases, studies of the susceptibility of organisms colonizing individuals can provide an indication of susceptibility of similar strains causing disease (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*). However, it should not be routinely assumed that such a relationship exists.

Absence of isolates

Empirical treatment without laboratory isolation of the causative organism and the use of non-cultural methods to diagnose infection present challenges to the surveillance of antimicrobial resistance. Where empirical treatment without laboratory isolation is the norm, active sentinel surveillance or special studies, including the collection and examination of clinical specimens, need to be considered.

Non-cultural diagnostic tests (e.g. antigen detection, PCR, etc.) are being used increasingly in clinical practice. Before genotypic methods can be used for the surveillance of resistance, consideration needs to be given to the extent to which genetic markers are consistent and predictable of phenotypic and clinical resistance.

Antimicrobial susceptibility tests

Antimicrobial susceptibility tests are undertaken to assist the clinician in selecting the most appropriate antimicrobial to use in the treatment of an individual patient suffering from infection. To accomplish this, appropriate specimens taken from the patient are submitted for culture. Organisms cultured from these specimens are further examined to determine the extent to which a particular drug inhibits the growth of the organism identified.

The methods normally used for susceptibility

tests are either the dilution test, which can be used to define the minimum inhibitory concentration (MIC) of the antimicrobial, or the diffusion test utilizing discs impregnated with the antimicrobial under examination. A variety of different test methods exist and WHO recommends that a quantitative method should be used. To assist the laboratory, a *Manual for the Laboratory Detection of Antimicrobial Resistance among Community Acquired Bacterial Pathogens of Public Health Concern in the Developing World* is available in draft (*8*). Internal quality control and external quality assurance must be incorporated into the laboratory routines, regardless of the test methods chosen.

Antimicrobials for surveillance

Since the primary reason for determining the susceptibility of organisms is to guide clinical management, the choice of drugs for surveillance needs to take this into account. In order to ensure that the requirement for data does not have an undue impact on laboratories, it is suggested that the number of antimicrobials for which susceptibility testing is requested for surveillance purposes should be three or at a maximum four, preferably coordinated between participating laboratories. Different antimicrobials will be necessary for different groups of organisms (e.g. Gram-positive and Gram-negative). In selecting such agents due account needs to be taken of those antimicrobials recommended for chemoprophylaxis as well as treatment.

Information outputs

The objective of surveillance is to provide information for action. Thus, the approach to surveillance will be determined by the nature of, and the timeliness with which the information is required. All surveillance systems need to be reviewed on a regular basis to ensure that they continue to address public health priorities and provide the relevant information needed by clinicians and policy-makers. It is important that the systems enable a clear distinction to be made between increases in prevalence of resistance resulting from improvements in compliance or changes in sampling procedure and those arising from real increases.

Developing plans for integrated surveillance of communicable disease and resistance

Developing an action plan

The key steps in developing plans for antimicrobial resistance surveillance are to identify:

1. For what purpose is information required?

The purpose of surveillance is to provide information for action. Before initiating the surveillance of antimicrobial resistance, the actions to be taken on the basis of surveillance information should be defined. The system can be designed so that the appropriate information is collected.

2. What needs to be done?

The objective is to draw up a priority list of surveillance activities that will lead to significant public health action. Two components that will need to be considered are:

- The priority diseases

- The priority antimicrobials

3. What is already being done?

The objective of a gap analysis is to identify:

- What systems are in place that provide integrated clinical and laboratory data on antimicrobial susceptibility?

- What systems are already in place that could be modified to secure integrated clinical and laboratory data on antimicrobial resistance?

- What systems need to be developed to fulfil the priorities identified?

4. What is achievable?

To identify what is practicable, consideration needs to be given to:

- Whether appropriate specimens can be obtained as part of routine management of patients suffering from the infection concerned

- Whether microbiological capacity exists to examine the specimens to the standards required. In doing so, decisions will need to be made as to whether specimens should be examined in a general microbiology laboratory or at a specialist reference laboratory which may be more distant from the site of patient care

- What type of surveillance is achievable and will it provide the information required for action.

5. What is the threshold level for action?

In the planning phase it is important to consider:

- At what frequency of resistance in a given pathogen is action to be taken?

- What percentage of cases of infection need to be caused by resistant organisms before action is taken?

- What are the criteria for increasing the surveillance activity from e.g. passive to active, or from sentinel to comprehensive?

In this context it is important to recognize that the changes in frequency of resistance which can be detected in a surveillance system depend on the number of isolates investigated and the frequency of resistance amongst these isolates. Table 1 provides a guideline when considering sample sizes in the preliminary phase of establishing a surveillance system.

6. What is the appropriate way of gathering such information?

Surveillance in itself does not control infection. The collection of data is time-consuming and has an opportunity cost. Whilst comprehensive surveillance may be appropriate for common infections caused by organisms where antimicrobial resistance is prevalent, it is unlikely to be appropriate to survey theoretical threats. In some circumstances, particularly with theoretical and potential threats, it may be sufficient to devise a system of monitoring the susceptibility of organisms submitted to reference laboratories. The objective of such monitoring will be to identify a pre-determined thresh-

old at which special studies or more extensive surveillance should be instituted.

7. What should be done with the results of surveillance?
When planning an integrated surveillance system, consideration needs to be given to defining:

- Who is responsible for disseminating the information?

- To whom should the information be given, at what time intervals and in what format?

- Are resources allocated for action?

Getting started

If there is no current antimicrobial resistance surveillance system in the country/region, one of the challenges will be to establish a network of laboratories and sufficient logistical support for the transfer of data and bacterial strains. Rather than aiming at a very extensive surveillance system, the chance of success is probably higher if the system is implemented on a smaller scale and expanded later. The following section provides examples of some basic surveillance that could provide a country or region with important information to describe the level of resistance in a limited number of pathogens of public health importance. The data, when analysed

and used for development of actions and interventions is valuable base-line information e.g. reviewing the recommendations for first-line treatment of common bacterial infections in the particular country or region under surveillance. When the basic surveillance system is operating effectively, other relevant pathogens may be added to the list, depending on local priorities.

TABLE 1. **ESTIMATE OF SAMPLE SIZES NEEDED FOR DOCUMENTING INCREASING ANTIMICROBIAL RESISTANCE FREQUENCIES**

% resistance detected in original sample	% resistance (indicative of significant increase) detectable in a second sample at sample sizes of				
	100	200	400	600	1000
2	9	7	5	4	3
5	14	11	9	8	7
10	21	17	15	14	12
25	39	35	32	31	28
50	65	60	58	56	54

The Table shows the resistance frequencies in sample one and two needed to be significant (p value = 0.05) at different resistance frequencies and sample sizes. As an example, if 5% of isolates in a sample of 200 is resistant in the first sample an increase to 11% or more in a second sample indicates a significant increase. By including more samples the significant increase is lowered and it can be calculated (Flemming Bager, personal communication).

Protocols for surveillance

Protocols for surveillance of antimicrobial resistance in bacterial infections of major public health importance are shown in Tables 2 and 3 with some further discussion in the notes below.

Diarrhoeal diseases

Diarrhoeal diseases are, in some parts of the world, a significant public health threat. In many cases treatment with antimicrobial agents is not needed, but for severe cases of shigellosis with *Shigella dysenteriae*, antimicrobial treatment is beneficial. In several resource-poor settings the frequency of resistance against the first-line drugs ampicillin and co-trimoxazole has risen to high levels. Thus, knowledge of the resistance frequencies will be of great value in making treatment recommendations. If specimens are taken from patients admitted to hospital, however, many of them will have received antimicrobial treatment prior to admission and this could lead to an overestimation of the resistance frequencies.

Respiratory tract infections

Acute respiratory tract diseases are one of the major causes of morbidity and mortality worldwide, particularly in children and a substantial part of total antimicrobial usage will be for treatment of these diseases. Because the total number of cases of pneumonia in a country or region is relatively high, a sentinel, episodic surveillance system is feasible. This surveillance system is active and enhanced; under normal circumstances you would not collect samples from all of these patients. This kind of surveillance system has several advantages. It makes it possible to limit specimen collection to the high incidence season for the disease. The duration of the sampling period will be shorter, which simplifies the logistics and maintains the enthusiasm of the data collectors. Only a subset of the primary health care facilities in the country need to participate, as long as they are representative of the population/cases as a whole. This reduces the number

of health care workers that require additional training for sample collection and lowers the risk for variation in the sampling methods. The small number of sampling sites makes it possible to establish a stable collaboration between the participating primary health care centres and the coordinating centre. This will be beneficial when subsequent sentinel sampling is conducted (e.g. the following year). Samples are taken from consecutive patients who attend the health care facility and fulfil the case definition. In children fulfilling WHO criteria for pneumonia, nasopharyngeal swabs are used instead of sputum samples. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the key pathogens to be isolated from the sputum samples, as they are the most frequent and relevant.

For surveillance purposes only a limited number of antimicrobials require susceptibility testing. Interpretation of data needs to be undertaken with particular caution since the correlation between penicillin resistance in *S. pneumoniae in vitro* and outcome of treatment of pneumonia is poor. However, *in vitro* results are a better guide for treatment recommendations regarding otitis media and meningitis.

Sexually transmitted infections

Most countries already have some surveillance activities for sexually transmitted infections. Clinics for Sexually Transmitted Infections (STI) may submit specimens to a National Reference Laboratory (NRL) for diagnostic testing. An existing system for transport of specimens from STI clinics to the laboratory and the dissemination of results and interpretations back to the clinics can be used for performing surveillance of antimicrobial resistance in *Neisseria gonorrhoeae*.

For surveillance of resistance in gonococci a sentinel, continuous, active enhanced surveillance system is proposed, using specimens already collected at the clinics. Participating STI clinics use the same case definition e.g. all first time untreated patients with penile or vaginal discharge. At the NRL sus-

ceptibility testing is performed on all isolates of *N. gonorrhoeae* meeting this definition. The participating sentinel centres should be representative to allow estimation of the frequency of resistant strains at the country or regional level. The sampling period is determined by the number of submitted specimens and the number of participating laboratories. For each country or region, the NRL selects the antimicrobials for susceptibility testing depending on the local distribution of resistance in gonococci and the antimicrobials recommended for treatment. In Table 3, tetracycline, penicillin, a third generation cephalosporin and ciprofloxacin are recommended.

Using data from hospital laboratories

Most hospitals have access to laboratory facilities for microbiological diagnosis. Many of these laboratories already perform some antimicrobial susceptibility testing of clinical specimens. However, at many hospitals, this information is used only for guiding treatment of individual patients, and is not kept in a format suitable for resistance surveillance. In some laboratories, records may not even be kept.

For surveillance purposes in the hospital setting, additional parameters to be added to the basic data set include: patient group and health care facility, day of admission (or whether the specimen has been taken >48 hours after admission, distinguishing community acquired and nosocomial infections) and, preferably, the antimicrobial treatment dur-

ing the hospital stay. The level of resistance in isolates collected at the hospital less than 48 hours after admission reflects resistance levels in the community e.g. in *E. coli* and *S. pneumoniae* blood stream isolates. The recommended 48 hour limit does not account for specimens originating from patients that had been transferred from another hospital.

If more than one isolate is recorded per patient, and the specimens are taken at different times, they should be registered separately in the database to be able to differentiate between existing resistance determinants at the time of instituting treatment and resistance emerged during treatment. For surveillance purposes the first, and only the first, isolate from each patient is used.

If the hospital laboratory already has a validated database, including the additional parameters, developing a surveillance system for the most common hospital infections is easily achievable. Relevant pathogens to be considered include *Pseudomonas aeroginosa*, *Klebsiella pneumoniae*, *E. coli* and/or *Staphylococcus aureus* from urinary tract infections, septicaemia and pneumonia cases. For assistance WHO has developed software for managing laboratory data called WHONET and a supporting software program for converting data in already existing databases to the WHONET-format called BACLINK. They can both be downloaded at

http://www.who.int/emc/WHONET/
WHONET.html

TABLE 2. **EXAMPLES OF INTEGRATED SURVEILLANCE OF COMMUNICABLE DISEASES AND ANTIMICROBIAL RESISTANCE**

Clinical syndrome/ presentation	Recommended case definition	Appropriate specimen	Optimal sampling location and surveillance type	Key pathogens
Acute diarrhoea	**Clinical**: Diarrhoeal illness with visible blood in stool **Lab**: Isolation of *Shigella dysenteriae* from stool	Faeces	Primary health care facility Sentinel	*Shigella dysenteriae*
Pneumonia	**Clinical**: Febrile illness with purulent productive cough; rapid breathing in children [1] **Lab**: Isolation of *Streptococcus pneumoniae* or *Haemophilus influenzae* from sputum or blood	Sputum, blood (nasopharyngeal swabs may be used in children)	Primary health care facility Sentinel	*Streptococcus pneumoniae, Haemophilus influenzae*
Bacteraemia/ septicaemia	**Clinical**: Sudden onset of fever; +/- petechial haemorrhages, purpuric rash, or rose spots **Lab**: Isolation of pathogen[2] from blood	Blood	Hospital Continuous	*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Salmonella typhi, Escherichia coli*
Meningitis	**Clinical**: Sudden onset of fever with neck stiffness or altered consciousness or other meningeal sign **Lab**: Isolation of pathogen from CSF (+/- from blood) or positive antigen test or Gram-negative diplococci present in centrifuged deposit of CSF	CSF, blood	Hospital Continuous	*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*
Urethral/vaginal discharge	**Clinical**: Urethral or vaginal discharge **Lab**: Gram-negative intracellular diplococci confirmed on culture as *Neisseria gonorrhoeae*	Urethral/vaginal swab	STI clinic Sentinel	*Neisseria gonorrhoeae*
Urinary tract infection (UTI)	**Clinical**: Frequency and dysuria or fever in presence of indwelling catheter or other focus of infection **Lab**: Isolation of *Escherichia coli* from urine in significant numbers[3] (or blood)	Urine (midstream or catheter specimen)	Primary health care facility Sentinel	*Escherichia coli*
Surgical wound infection	**Clinical**: Pus in wound +/- fever **Lab**: *Staphylococcus aureus* or *Streptococcus pyogenes* isolated on culture[4]	Pus or wound swab	Hospital Continuous	*Staphylococcus aureus*
Hospital-acquired UTI, septicaemia, pneumonia	**Clinical**: see above **Lab**: Isolation of *Staphylococcus aureus, E. coli, Pseudomonas aeruginosa* or *Klebsiella pneumoniae*[5]	Urine, blood, sputum, pus from any infected site	Hospital Continuous	*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*

1: See Guidelines for Diagnosis of Pneumonia in Children (*10*); 2: Any pathogen isolated from blood culture may be significant; the most important examples are given here; 3: >10[5] in midstream (clean-catch) urine specimen; 4: Other pathogens may also cause wound infections but *S. aureus* is the most important in terms of resistance surveillance; 5: Other pathogens may be the cause of hospital-acquired infections; these are considered as useful indicators for resistance surveillance purposes.

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TABLE 3. **ANTIMICROBIAL RESISTANCE SURVEILLANCE OF KEY PATHOGENS**

Key pathogens	Antimicrobials to be tested for surveillance purposes	Recommended minimum data set	Recommended analyses of data on antimicrobial resistance	Further information
Shigella dysenteriae	Ampicillin, chloramphenicol, co-trimoxazole, nalidixic acid	**Case-based data**: Unique identifier capable of cross-linkage with lab data; Age or date of birth, gender; Place of residence; Presenting signs/symptoms and Date of onset; Outcome (recovery, death). **Lab-based data**: Unique identifier capable of cross-linkage with clinical data; Specimen date and type; Resistance to specified antimicrobials.	For susceptible and resistant confirmed cases: Number of cases by age, gender and geographical area by week; Number of deaths; Routine aggregation of antimicrobial resistance centrally with regular (monthly) publication and dissemination.	Laboratory methods for the diagnosis of epidemic dysentery and cholera (*9*).
Streptococcus pneumoniae	Oxacillin, ampicillin, erythromycin, chloramphenicol, co-trimoxazole	**Case-based data**: As for *Shigella dysenteriae* + vaccination history. **Lab-based data**: As for *Shigella dysenteriae*.	Number of suspected and confirmed cases (resistant and susceptible) by syndrome, age, gender and time period in defined population.	Monitoring of resistance of specific serotypes of *Streptococcus pneumoniae* may need to be considered in the evaluation of immunization programmes. Isolates made from nasopharyngeal swabs may be considered as surrogates for infecting strains.
Haemophilus influenzae	Ampicillin, erythromycin, chloramphenicol, co-trimoxazole	**Case-based data**: As for *Shigella dysenteriae* + vaccination history. **Lab-based data**: As for *Shigella dysenteriae*.	Number of suspected and confirmed cases (resistant and susceptible) by syndrome, age, gender and time period in defined population.	
Staphylococcus aureus	Penicillin, oxacillin	**Case-based data**: Unique identifier capable of cross-linkage with lab data; Age or date of birth, gender; Health care facility and care group; Date of admission and of onset; Presenting signs/symptoms; Predisposing factors, e.g. surgery, trauma, indwelling devices. **Lab-based data**: Unique identifier capable of cross-linkage with clinical data; Specimen date and type; Method of identification of *Staphylococcus aureus*; Resistance to specified antimicrobials.	Incidence rates of infections (denominator e.g. bed days, admissions) due to susceptible and resistant strains within and between care groups and type of institution. Incidence rates by predisposing factors; Comparison between community and hospital-acquired infections.	
Salmonella typhi	Ampicillin, chloramphenicol, co-trimoxazole, ceftriaxone, ciprofloxacin	**Case-based data**: As for *Shigella dysenteriae*. **Lab-based data**: As for *Shigella dysenteriae*.	As for *Shigella dysenteriae*.	
Escherichia coli	Ampicillin, co-trimoxazole, gentamicin	**Case-based data**: Unique identifier capable of cross-linkage with lab data; Age or date of birth, gender; Health care facility and care group; Date of admission and of onset. **Lab-based data**: As for *Shigella dysenteriae*.	Incidence rates of infections (denominator e.g. bed days, admissions) due to susceptible and resistant strains within and between care groups and type of institution. Comparison between community and hospital-acquired infections.	The susceptibility patterns in non-hospital acquired isolates reflects to some degree the resistance in the commensal flora.
Neisseria meningitidis	Penicillin, chloramphenicol	**Case-based data**: As for *Shigella dysenteriae*. **Lab-based data**: As for *Shigella dysenteriae* + method of identification of *N. meningitidis*.	Monthly aggregate of incidence rates of infections due to all isolates (susceptible and resistant).	Beta-lactamase production has been reported in *N. meningitidis*. Although very rare, penicillin-resistant strains should be checked for beta-lactamase production.

TABLE 3. **ANTIMICROBIAL RESISTANCE SURVEILLANCE OF KEY PATHOGENS** *(continued)*

Key pathogens	Antimicrobials to be tested for surveillance purposes	Recommended minimum data set	Recommended analyses of data on antimicrobial resistance	Further information
Neisseria gonorrhoeae	Penicillin, tetracycline, ceftriaxone, ciprofloxacin	**Case-based data**: Unique identifier capable of cross-linkage with lab data; Age or date of birth, gender; Risk behaviours; Date of onset of symptoms. **Lab-based data**: Unique identifier capable of cross-linkage with clinical data; Specimen date and anatomic site sampled; Resistance to specified antimicrobials.	Number of confirmed and suspected cases (susceptible and resistant) by month by sentinel site, anatomic site, age, gender and risk behaviour.	Further guidelines on management of STIs can be accessed at http://www.who.int/emc-documents/
Pseudomonas aeruginosa *Klebsiella pneumoniae*	Gentamicin, ceftazidime	**Case-based data**: Unique identifier capable of cross-linkage with lab data; Age or date of birth, gender; Health care facility and care group; Date of admission and of onset; Presenting signs/symptoms; Predisposing factors, e.g. trauma, burns, catheterization, intubation. **Lab-based data**: Unique identifier capable of cross-linkage with clinical data; Specimen date and type; Resistance to specified antimicrobials.	Incidence rates of infections (denominator e.g. bed days, admissions) due to susceptible and resistant strains within and between care groups and type of institution.	These two species are suggested as representative of Gram-negative hospital pathogens; others may be included according to local circumstances.

TABLE 4. **SUMMARY OF ANTIMICROBIALS FOR ANTIMICROBIAL RESISTANCE SURVEILLANCE TESTING**

Antimicrobial	Significance
Tetracycline	Representative of members of this group, except minocycline
Chloramphenicol	Results may be extrapolated to thiamphenicol
Ampicillin	Representative of broad spectrum penicillins susceptible to beta-lactamase
Benzyl penicillin	Tests susceptibility to all beta- lactamase-susceptible penicillins
Oxacillin	Representative of the whole group of beta-lactamase-resistant penicillins
Ceftriaxone; ceftazidime	Representatives of third generation cephalosporins
Co-trimoxazole	Representative of trimethoprim alone and in combination with sulphonamide
Erythromycin	May be used to indicate susceptibility to certain other macrolides (azithromycin, clarithromycin)
Gentamicin	Should be used for primary testing of susceptibility to other aminoglycosides
Nalidixic acid	Quinolone resistance
Ciprofloxacin	Fluoroquinolone resistance

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