
# Framework for Use of Antimicrobial Resistance Surveillance in the Development of Standard Treatment Guidelines

**Prepared by**
**The Alliance for the Prudent Use of Antibiotics**

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## 1. Introduction

A patient with a fever and a certain set of physical signs and symptoms comes to a caregiver. Whether the caregiver is a physician trained in infectious diseases working in a fully equipped medical center in a rich country or a health care worker at a remote outpost in a country with limited resources the problem will be similar. Either may begin supportive measures, most-importantly perhaps re-hydration. Neither will know for certain at the outset when treatment decisions have to be made, however, whether bacteria are infecting the patient, whether those bacteria need to be treated or to which antimicrobial agents they are already resistant.

Each of these caregivers needs decision-support for making such choices about use of antimicrobial agents. That decision-support can be seen as all the information available to improve a caregiver's estimates of the probabilities that a patient's infection is due to one or another kind of bacteria and the probabilities of each of those kinds of bacteria at that time and place being susceptible to each of the antimicrobial agents available there.

STGs are derived from decision-support information and may be seen as its distillation for the busy, decision-making caregiver. STGs for infectious diseases outline the preferred drug and non-drug treatments for those infectious diseases commonly seen in a specific health system. They have been shown to improve the rational use of drugs. STGs also serve as a basis for educating caregivers, evaluating programs, and managing procurement and distribution of drugs. Their potential benefits include improvements in patient outcomes, drug availability and cost savings. Health authorities may measure compliance with STGs to assess clinical practices, to focus interventions on identified deficiencies and to assess the effect of interventions on performance indicators.

In developing STGs, national Drugs and Therapeutics Committee (DTC) or other policy-making body should review similar, available documents prepared by other national, and international scientific and clinical groups. These may include STGs from other countries in the region, recommendations from textbooks of infectious diseases [1, 2] and guidelines prepared by professional societies such as the Infectious Diseases Society of America [3], the International Union for Tuberculosis and Lung Diseases [4, 5], the World Health Organization [6, 7] and others [8]. For the treatment of several common infections, a useful set of publications to consult is the *WHO Model Prescribing*

*Information* Series, in particular the document *Drugs used for bacterial infections* [9].

Unlike STGs for other kinds of disease, such as hypertension or congestive heart failure, STGs for infectious diseases need ongoing decision-support-based modification for time and place. Modification is needed because, as emphasized above, both the incidence of infection with various kinds of microorganisms and the resistance of each kind to antimicrobials varies greatly with time and place. Similarly, the prevalence of resistance to any antimicrobial agent may vary greatly between bacteria of any one kind at different times and places. Strains of *Staphylococcus aureus* resistant to methicillin (MRSA) or of *Streptococcus pneumoniae* resistant to penicillin were widespread in hospitals and in the community, respectively, in Europe for a decade or more before they began to appear in North America. Conversely, vancomycin-resistant enterococci, which appeared and became widespread in hospitals in the U.S. during the last decade, are rarely isolated from humans elsewhere. Prevalence of resistance to chloramphenicol may vary tenfold between countries.

When and on what basis a standard antibiotic treatment regimen or guideline should be changed can be informed by surveillance data. Antimicrobial resistance (AMR) data can improve standard treatment guidelines (STGs) in Nepal, but first it is necessary to devise a method in which to incorporate this data into the process of revising and updating the STGs.

## 1.1 Objectives

- To develop a tool to guide the national Standard Treatment Guidelines (STG) committees and hospital Drug and Therapeutic committees (DTC) in the use of AMR surveillance data for adapting standard treatment guidelines.
- To provide an easy-to-use decision guide for the national Standard Treatment Guidelines (STG) committee and hospital Drugs and Therapeutics committees (DTC) in the appropriate use of antimicrobial resistance (AMR) surveillance data for the adaptation of STGs.

## 2. Antimicrobial resistance

The target of antimicrobial therapy is bacterial populations rather than human cell physiology, as would be the case for medications such as insulin and anti-hypertensives. Consequently there are a number of issues specific to antimicrobials which must be highlighted. Most important among these is the emergence and spread of microbes resistant to the antimicrobials upon which we have come to depend [10-12]. Consequences include:

- Decreased efficacy over time. The efficacy of drugs used for diseases of human physiology remains unchanged over time. So in the

development of non-antimicrobial agents, researchers can aim to develop compounds which are safer, more efficacious, and more convenient. In the development of antimicrobials, however, industry must additionally and continuously strive to identify agents which have efficacy at least equal to those of past compounds.

- Variables rates of resistance and efficacy. The frequency of resistant bacteria may differ markedly between individuals in a community and between geographic and demographic populations. Consequently, one global set of treatment recommendations would be ineffective and inappropriate.

- Compromised clinical outcome. In predicting a patient's clinical outcome, clinicians must consider not only disease severity (a pathophysiological parameter) but also the level of activity of the drug against the infecting organism (a therapeutic parameter). As a result, even the treatment of relatively minor infections due to resistant organisms may be unsuccessful or require the use of expensive intravenous agents to achieve cure.

- Spread of resistant strains. Drug use and misuse in an individual effects everyone. Because of the persistence and spread of resistant microbes, use of an antimicrobial anywhere can negatively impact the value of the drug around the world and to future generations. In contrast, improper use of non-antimicrobial compounds generally impacts only the individual receiving treatment.

- Impacts on disease epidemiology: Antimicrobial use in an individual impacts all microbial strains present -- susceptible and resistant, colonizing and infecting, bacterial and nonbacterial -- disrupting the usual dynamics and interrelationships between populations. In consequence, antimicrobial use has had a major impact on shaping the etiologies and characteristics of pathogens causing human disease.

## 3. Surveillance of antimicrobial resistance

## 3.2 Objectives of an antimicrobial resistance surveillance program

The *WHO Global Strategy for Containment of Antimicrobial Resistance* recognizes as one of two "fundamental priorities" the need to "designate or develop reference microbiology laboratory facilities to coordinate epidemiologically sound surveillance of antimicrobial resistance" [13]. Surveillance data are required in the development of strategies to contain resistance and to measure the impact of interventions [14]; [10]; [15]; [16].

The objectives, organization, and activities of national antimicrobial resistance surveillance programs should reflect identified public health priorities, available resources and expertise, and intended interventions utilizing the surveillance data [17, 18]. Objectives of a national surveillance collaboration may address the following:

- characterization of disease etiologies and resistance trends
- prompt identification and investigation of new threats in resistance
- guidance to policy-makers in developing therapy recommendations
- guidance to public health authorities in responding to outbreaks of community and hospital outbreaks of resistant organisms
- evaluation of the impact of therapy and infection control interventions on infection rates and cure rates
- strengthening of laboratory capacity and national communicable disease infrastructure through a process of continuous quality improvement

All of these objectives target important needs in a national resistance containment strategy -- improving the quality of patient care, responding to new problems quickly, understanding the processes by which resistance emerges and spreads in a country. It should be clear that establishing local and national therapy guidelines is but one of several important goals of a surveillance program. Bodies responsible for the development of STGs thus must understand the organization, objectives, strengths, and limitations of existing surveillance programs in order to evaluate the relevance of available data to guiding therapy recommendations. Conversely, national authorities should be able to indicate to surveillance coordinators the kind of data which may be required to inform the policy-making process.

Surveillance programs provide invaluable insights into the problems of resistance emergence and spread, but translating this knowledge into strategies to contain resistance requires close, collegial, and detailed discussions among a variety of groups with different types of expertise [19]. Thus to fully achieve the objectives established by a surveillance program, appropriate links between surveillance groups and local and national authorities must be established and strengthened. Relevant groups may include national authorities, media representatives, patient advocacy groups, industry partners, international agencies, and professional societies of microbiologists, pharmacists, prescribers, and infection control personnel.

## 3.3 Strategies for surveillance of antimicrobial resistance

There are a variety of strategies by which surveillance programs can choose to collect and test clinical specimens [17, 18] [20]. In practice, a combination of complementary strategies coordinated by one or more institutions is often appropriate to achieve national surveillance objectives. Groups developing and

updating STGs need to understand the limitations and strengths of these approaches as they try to translate resistance findings into policy recommendations.

*Alert organism surveillance*: At a minimum, all countries should have a system in place for identifying, transporting, and confirming novel or important resistance results. Findings may have global import, such as fluoroquinolone-resistant *Salmonella* Typhi, vancomycin-resistant *Staphylococcus aureus*, or penicillin-resistant Group A streptococci. Others may be important for a specific country or region, for example ESBL-producing *Escherichia coli* or vancomycin-resistant enterococci. Following confirmation by national and/or international centers, there should be mechanisms for disseminating information on these strains to national authorities, clinicians and microbiologists, and the international scientific community, as appropriate. Actions undertaken may include interventions to limit the spread of the resistant strain, educational efforts targeted at microbiologists and clinicians, or the organization of targeted surveys to investigate the epidemiology of the resistant strain more fully.

Advantages: Such a system is inexpensive, relying principally on alert, informed, and motivated microbiologists attentive to findings of public health importance. National coordinators may wish to make a list of certain resistance findings which should not be reported to clinicians without confirmation at the national level.

Disadvantages: Alert systems can document the presence of important strains in a country. However, it provides little information on how common such strains are, so cannot be used for guiding treatment policies.

*Comprehensive surveillance of routine specimens from clinical laboratories*: In the course of their routine work, laboratories worldwide process large numbers of diagnostic specimens to support clinical decision-making. National authorities should take advantage of this resource for achieving public health objectives.

Advantages: Systematic review of routinely generated data provides an invaluable insight into the changing patterns of disease and resistance epidemiology, including the identification and characterization of unexpected problems (in laboratory testing quality, in outbreaks, in new resistance phenotypes) and the monitoring of long-term trends. Such systems are relatively inexpensive and sustainable once laboratories have been established. Since the data already exist, it is incumbent on authorities to review the available laboratory findings.

Disadvantages: As clinical specimens are not collected with the specific aim of directing therapy guidelines, accumulated data need to be interpreted carefully when used for this purpose. Biases in collection practices are common (described in further detail in the next section), particularly in issues of outpatient therapy where most therapy is done empirically without the benefit of a diagnostic culture.

*Targeted surveillance of priority issues in clinical laboratories*. To redress some of the potential problems seen with routinely generated data, surveillance program coordinators may wish to identify a few priority issues which merit a specific ongoing program of data collection. Examples include: a biannual survey of uncomplicated urinary tract infections in young women; systematic quarterly sampling of patients presenting with urethral discharge; monthly centralized serotyping of 20 *Salmonella* isolates from each institution participating in the network. In targeted surveillance programs, there is often a formal protocol describing criteria for patient selection and specimen collection, specimen processing, and information to be collected.

A well-designed targeted surveillance protocol can complement routinely generated data in a number of ways. Findings from the targeted approach may support the findings from the routine surveillance strategy, thereby validating conclusions generated from the routine data. Alternatively, the targeted approach may suggest that routinely generated data are unreliable for certain applications.

Advantages: It may be possible to minimize biases through defined criteria for patient and specimen selection; patient information not routinely available can be collected, such as risk factors, demographics, and clinical outcomes; laboratory tests not routinely performed may be incorporated. A carefully developed protocol addressing the public health relevance of resistance estimates can assist policy makers in the development of STGs.

Disadvantages: Targeted surveillance strategies are often expensive and labor-intensive with significant concerns for long-term sustainability. Only a few priority issues are studies, so no information is available on other important public health concerns, including new challenges which may go unrecognized. Many targeted surveillance programs, in fact, do rely on routinely collected specimens, as funds are not available for the collection of additional patient specimens. While such protocols can be of great value for certain applications, they do not solve the important issue of biases introduced as a result of select patient sampling and testing.

*Surveillance of national reference center isolate collections*: The above-described strategies apply especially to surveillance programs which rely on microbiological testing performed by institutions participating in a national surveillance network. An alternative approach is to use test results obtained in a national reference center. Reference laboratories generally process a diverse set of isolates for a variety of indications: centralized collection of certain organisms of public health importance, for example *M. tuberculosis*; centralized performance of specialized microbiological tests, such as serotyping; confirmation and characterization of "difficult" or "unusual" isolates.

Advantages: Centralized testing of isolates has several advantages: greater resources and capability to perform specialized laboratory tests; standardization and efficient use of test methodologies; greater microbiological and epidemiological expertise available; links to other national bodies, such as policy-making groups.

Disadvantages: For many organisms, there may be no defined criteria for sending isolates to the national center. Consequently, national strain collections often exhibit extreme biases, for example in resistance characteristics. For organisms in which testing is principally centralized, for example *M. tuberculosis*, the national collection may perhaps be more representative of the national picture. Thus if national strain collections are to be used in developing therapy guidelines, STG committees must evaluate the epidemiological relevance of resistance statistics obtained.

*Special surveys*: Special surveys have many of the characteristics of the target surveillance strategies described above. The distinction is that special surveys are organized as time-limited investigations, and are not intended to be repeated over time. They are thus not truly "surveillance" programs in the sense of an ongoing collection and analysis of public health information. The majority of surveillance reports which appear in the international literature are of this type.

Advantages: Special surveys can be used to obtain a snap-shot of specific priority issues in disease epidemiology or resistance. As described for targeted surveillance programs, special surveys can address a variety of importance scientific, therapeutic, or public health questions. If a special survey is found to be of value, surveillance coordinators may aim to incorporate the survey protocol into an ongoing targeted surveillance program.

Disadvantages: As described for targeted surveillance strategies, special surveys are often expensive and labor-intensive, and provide a detailed snap-shot of only a limited number of clinical concerns. Consequently,

it is not possible to draw conclusions about trends, populations not included in the study, or other organisms. Given differences between protocols, comparability to other relevant studies is often difficult to ascertain.

In short, national policy makers should be aware of the types of laboratory data which are available in their country. At a minimum, all countries should have an alert system for confirming strains of recognized public health importance and a national reference laboratory with expertise in clinical, laboratory, and epidemiological aspects of antimicrobial resistance issues. Countries are also strongly encouraged to systematically review routinely generated results for a number of applications: identification of new problems, such as new strains or outbreaks; establishment of baseline trends in organism frequencies and resistance; improving the quality of microbiological testing through feedback to laboratories on potential problems identified. If the routinely generated information for certain conditions is considered to be unreliable or of questionable relevance to the establishment of treatment guidelines, resources should be mobilized for designed time-limited special surveys or ongoing targeted surveillance programs to support the decision-making process.

## 4. Data quality and biases

In using laboratory data to guide STG formulation, policy makers must consider two critical issues: 1. microbiological data quality; and 2. epidemiological relevance [21].

### *Quality assurance in laboratory testing*

The first question which must be addressed is whether the laboratory is providing reliable information on the specimens processed. Quality assurance strategies must cover all aspects of specimen processing, storage, workup, test performance, interpretation, and communication. To this end, many laboratories have developed or adapted Standard Operating Procedures for the processing of clinical specimens [22] [23, 24]. With respect to resistance surveillance studies, of particular concern are the reliability of the organism identification and the antimicrobial susceptibility test results. The U.S. National Committee for Clinical Laboratory Standards [25, 26] and other reference-making bodies [27-30] have well-described guidelines for how laboratories should ensure the quality of test reagents, test performance, and test interpretation. Internal quality control procedures generally include frequent testing of standardized strains and monitoring the tests results of clinical isolates for biological plausibility. Participating in external quality assurance schemes [18, 31-40] is also a valuable educational and, in some

countries, regulatory activity in ensuring a laboratory's capacity to detect important resistances.

Interventions to improve the quality of laboratory test performance include training activities, site visits and audits, feedback on results collected, and educational news bulletins. Problems in the quality of test reagents must also be reviewed. At a minimum, laboratories should be able to evaluate the quality of the reagents which they are using and to implement guidelines on the proper storage and handling of these materials. If problems in reagent quality are identified in reagents arriving in the laboratory, discussions with the manufacturer and shippers may be necessary to diagnose and rectify the problems.

## *Epidemiological relevance*

If the quality of laboratory testing is acceptable, then resistance estimates provide a useful measurement of resistance in organisms isolated from patients presenting to medical care from whom specimens were taken and from which a laboratory was able to obtain an isolate for which a susceptibility test was performed. But how relevant are such estimates to patients who do not seek medical care and from whom clinical specimens are not taken? There are several levels at which important biases in resistance estimates can be introduced.

- Patients: Which individuals seek out medical care? Demographic considerations include the patient's financial or insurance status, geographic origin, age, sex, ethnicity, occupation, and location of the health center. With respect to clinical issues, do patients with more severe disease seek care? those who fail self-administered therapy? Are the resistance characteristics of outbreak strains similar to those of endemic strains?

- Specimen collection: From which patients do physicians collect diagnostic specimens? Factors to consider include the patient's financial or insurance status, recognized underlying patient risk factors, severity of illness, and failure to respond to previous therapy.

- Laboratory testing: What organisms can the laboratory reliably isolate and identify? What are the laboratory's practices for antimicrobial susceptibility testing, for example are all relevant antimicrobials tested against all isolates? against isolates causing invasive disease? Are second-line antimicrobials only tested against isolates with resistance found to first-line agents?

- Data analysis: Are resistance estimates stratified by relevant factors, such as inpatient *vs.* outpatient origin, pediatric *vs.* adult, diagnostic

*vs.* screening sample, endemic *vs.* epidemic strains? Is there a mechanism for handling "repeat" isolates, *i.e.* multiple isolations of a given organism from a particular patient?

## *Developing a surveillance protocol.*

In the design of protocols for targeted surveillance and special surveys, researchers have an opportunity to minimize potential biases by defining steps for obtaining a sample representative of the population for which the STG is being developed. Where feasible, surveillance program coordinators may wish to define criteria for patient selection, provide funding for collection of specimens in all enrolled patients, and describe the use of defined panels of antimicrobials to be tested against all isolates. Unfortunately, obtaining a truly representative sample may be prohibitively expensive or logistically difficult, particularly on an ongoing basis, so surveillance coordinators must continue to consider potential biases when analyzing and interpreting findings.

## *Data analysis and interpretation.*

When interpreting any available data -- from routine or targeted surveillance programs, from clinical laboratories or national reference centers -- issues of bias in data interpretation are paramount. Rather than ask whether a particular resistance estimate is "correct" or not, we should presume that the statistic is "correct" for the specimens collected (presuming that laboratory test results are reliable), but we need to ascertain and describe the population for which these estimates are relevant. This can be done through analysis of the available demographic data and review of the process by which specimens were taken. A description of the population may be as simple as "the subset of patients presenting to the health center from which urine cultures were collected" or "the first 10 men in each quarter presenting to the health center with urethral discharge". A more complete description may include the percentage of patients with similar symptoms from which specimens were taken and informal impressions or formal assessments as to why specimens were collected from some patients but not from others.

After describing the population on which the resistance estimates are based, policy-makers must assess whether resistance estimates are relevant to the population for which they are developing guidelines. "Relevant" estimates need not necessarily mean "identical" estimates. Given financial and logistic realities, well-designed protocols with representative sampling and testing of selected patient populations are often not feasible, particularly on an ongoing basis for multiple clinical syndromes. Policy makers should thus consider whether available data are of some value in guiding decisions for the STG, even if the precise estimate of resistance is biased with respect to the target population. Even in the presence of potential bias, results can be used for the

following: description of resistance phenotypes which have been identified in the country; assessment whether resistance is relatively common or uncommon for various antimicrobials; comparison of the relative frequency of resistance between therapeutic alternatives; temporal trends in resistance which may parallel trends in resistance in the target population; and the relative frequency of various etiologies causing disease.

Given the uncertainties in the influence of potential biases on resistance estimates, surveillance groups may wish to supplement their usual surveillance activities (*e.g.* with routine or targeted surveillance) with occasional validation studies to ascertain whether significant bias in estimates actually exist and if so whether there is a consistent relationship between estimates obtained by the two approaches.

In order to implement a comprehensive resistance containment strategy, it has previously been noted that surveillance programs often have several objectives besides the development of therapy guidelines, for example the identification and confirmation of new resistance threats, prompt recognition of and response to hospital or community disease outbreaks, and strengthening of laboratory capacity for supporting individual patient care decisions and for supporting public health interventions. Surveillance data continue to provide a great support to these objectives, despite potential biases in resistance estimates.

## 5. Use of resistance data to guide therapy recommendations

### *Considerations*

*If use of an antimicrobial is indicated in the treatment of a specific disease and if resistance is an important consideration, by what process should policy makers make the selection of antimicrobials for use in the STG?*

There is no simple answer to this question. In short, a balance must be sought between the resources available and the aim of providing an acceptable level of health care both in the short- and long-terms. Policy makers must also seek a compromise between possible conflicts in the treatment needs of individual patients and of the overall population.

For each disease considered, the objectives of antimicrobial treatment should defined. It should be remembered that for many common bacterial infections, relatively healthy patients with intact immune systems will eventually recover, even in the absence of antimicrobial therapy. Thus therapy objectives may include: decreasing patient suffering (disease severity and duration), preventing short-term complications and long-term morbidity, saving lives in the severely ill, and limiting transmission of infection to patient contacts. In

some instances, national STGs may be appropriate, for example in the treatment of many outpatient conditions. In others (hospital-acquired infections, specific patient subpopulations), locally developed STGs may be more appropriate.

In deciding whether and which antimicrobial should be recommended for individual patients and for the STG, a number of parameters should be considered:

*Clinical*

- patient demographic factors (age, sex, pregnancy, geographic origin, recent hospitalization, *etc.*) which may impact therapeutic decisions, disease pathophysiology, and resistance rates
- severity of patient illness
- underlying conditions compromising the patient's immune system
- consequences of treatment failure: discomfort, absenteeism, complications, long-term sequelae, death
- availability and likelihood of follow-up in the event of treatment failure

*Pharmacological*

- drug efficacy and availability of alternatives
- toxicities and side effects, including the need for patient monitoring and laboratory testing
- expected compliance with prescribed treatment (dosing, duration of therapy)

*Microbiological*

- the frequency of various pathogens causing the disease in the local setting
- impact of resistance of clinical outcome
- rates and trends of antimicrobial resistance in the patient population, in the region, and in the world

*Public health*

- available resources for antimicrobials and diagnostic laboratory support
- prevention of disease transmission
- antimicrobial selection pressure for resistant organisms

## 6. Resistance surveillance and therapy decisions

*How can antimicrobial resistance data be used to guide therapy recommendations? When should current antimicrobial recommendations, i.e. STGs, be changed?*

There is no widely accepted consensus on how to apply resistance data to therapy decisions. However, there is agreement that any recommendation must be a compromise between the availability of health resources and therapeutic alternatives, rates of successful clinical outcomes, and pressure for the ongoing selection of resistant organisms. The relative importance of each of these factors is crucial, and will differ from country to country.

A number of factors must be balanced when a decision is considered to switch from a currently used first-line agent to an alternative regimen: In deciding among various agents, the following questions should be considered:
Unfortunately data are lacking for many important diseases:
What are the economic and logistical implications and expected clinical efficacy of various alternative therapies?

- What percent of patients recover in the absence of antimicrobial therapy?
- What are the public health and economic costs associated with treatment failures under the current recommendation?
- If a currently recognized "reserve" agent is recommended for widespread use as a first-line option, will there be additional options available as resistance to it emerges?
- For each alternative agent:
  - what percent of bacteria are resistant?
  - what is the impact of resistance on clinical outcome?
  - what is the likelihood of resistance emergence?
  - are there other important clinical conditions for which this antimicrobial is an important first-line or reserve agent? if resistance does emerge, will there be other options for treating those conditions?
  - what is the cost of the agent and are there special concerns regarding side effects or monitoring needs?
- How likely and quickly will resistance develop to the alternative agents?

A number of strategies for using surveillance data to guide therapy recommendations have been described. The following are four methods that could be employed by the STG and DTC committees in Nepal. They are not mutually exclusive; in fact, they are complementary.

## *6. 1. Periodic formal review of resistance estimates and treatment recommendations*

Relevant groups (both at the health facility and national level) gather to discuss the adequacy of STG recommendations and of the compliance by care-

givers with STG recommendations. At the national level, such groups may include microbiologists, clinicians and infectious disease specialists, pharmacists, public health epidemiologists, and national regulators. For each STG under consideration, this group should review available materials on disease etiologies and resistance estimates, reports of treatment failures, requests for specific STG modifications, and information on newly available compounds.

As detailed in Section 5 under *Considerations*, the decision to switch from one antimicrobial to another is a complicated one, and can generally not be made solely on the basis of resistance thresholds. Issues of cost, consequences of non-treatment or ineffective treatment, correlation between laboratory resistance and clinical outcome, biases in resistance estimates, and overuse of reserve agents must be balanced.

In the treatment of severely ill patients, acceptable rates of treatment failure, including death, are necessarily lower than for the treatment of non-life-threatening conditions in relatively healthy individuals, many of whom may indeed recover without antimicrobials. For treatment of the severely ill, clinicians will generally want to use agents available with the lowest observed rates of resistance, irrespective of the absolute percent resistance. For less severe illness, much higher rates of resistance to first-line agents may still be compatible with an overall acceptable level of health outcome. Unfortunately, what is considered "acceptable" in terms of rates of treatment failure, relapse, and death will need to be balanced against what is achievable with the resources available.

In practice, such review bodies may focus principally on comparisons of relative rates of resistance between relevant compounds, rather than absolute rates. However, if resistance rates for first-line agents are relatively high (to be defined separately for each clinical scenario), clinicians and public health officials should be particularly attentive to the importance of monitoring treatment failures and the potential need to revise formularies and treatment recommendations.

## *6. 2. Resistance alert thresholds*

*What percent resistant is consistent with acceptable rates of treatment failure? At what percent resistant should antimicrobial treatment guidelines be modified?*

For most clinical scenarios there are inadequate data to support solid evidence-based recommendations. Rather, educated proposals of experts in the field familiar with the clinical, microbiological, and epidemiological issues have been put forward. Subsequent experience has supported the use of some

thresholds as reasonable guidelines for achieving acceptable clinical results over time.

Resistance thresholds derived from clinical efficacy studies or decision analysis algorithms are described in Sections 3 *Clinical surveys -- monitoring of treatment outcome* and 4 *Decision Analysis*. Such approaches highlight the point that to be meaningful and practical, resistance thresholds should reflect the local epidemiology of disease etiologies, health-care infrastructure, and financial resources. Thus for many conditions, globally relevant thresholds for action will not be feasible. For a few diseases, some recommendations for action thresholds have been proposed by international bodies and may serve as a reference point against which national recommendations should be compared.

The use of an empiric threshold for resistance in the development of guidelines for the treatment of gonococcal infections is frequently cited and highlights a number of important principles. 1) Infection with *N. gonorrhea* (symptomatic urethritis in men, symptomatic or asymptomatic infection in women) is unlikely to clear spontaneously. Additionally, further transmission of the organism if initial therapy fails is an important public health concern. Therefore, effective empiric treatment which minimizes the risk of treatment failure or relapse is always indicated. 2) Clinical outcome is closely correlated with laboratory susceptibility test results: susceptible strains generally respond to therapy, while resistant strains do not. Consequently laboratory-based resistance estimates of representative clinical isolates of *N. gonorrhoeae* should correlate well with treatment failure rates.

A recommendation of 5% as a resistance threshold has thus been recommended by WHO and others and widely used for guiding selection of antimicrobials to treat gonorrhea [41]. Though the origin of 5% as a proposal is unclear, the implication is that first-line therapy recommendations should be able to successfully treat at least 95% of cases of gonorrhea, whereas close to 0% of patients would resolve their infections spontaneously. If resistance to a first-line agent rises above 5%, then switching to an alternative, more effective agent is warranted. In resource-wealthy settings, a threshold of 3% has also been suggested [42]. A similar empiric recommendation has been proposed by WHO for the treatment of meningitis due to *Streptococcus pneumoniae* [43]. If 10% or greater of *S. pneumoniae* isolates from cases of meningitis are due to penicillin-intermediate strains, initial empiric therapy should be vancomycin with ceftriaxone or cefotaxime rather than with penicillin [44-46]. It is important to highlight that when available local and/or regional resistance prevalence rates should guide empirical treatment of lower respiratory infections due to *S. pneumoniae, H. influenzae and M. catarrhalis* [3]. In addition, study sponsored by ANSORP [47]among 11 Asian countries, Korea (Seoul), Japan (Nagasaki), Vietnam (Ho Chi Minh City), and Thailand (Bangkok) showed *S. pneumoniae* (isolates were recovered from clinical specimens

representative of normally sterile body sites), with alarmingly high prevalence of penicillin resistance (>50%). Thresholds have also been used for several years in establishing guidelines for tuberculosis therapy but in recent years [48] there has been a shift in emphasis towards individualized therapy as described in the DOTS-Plus strategy [49].

In case of malaria, the WHO recommends a change in first-line therapy when an arbitrary figure of 25% of patients treated experience reappearance of infection [50]. For TB, a multi-drug therapy with rifampin, pyrazinamide, isoniazid, and either ethambutol or streptomycin is required when resistance prevalence rate to isoniazid is >4% [51]; if multidrug resistance exceeds 9.6% in the USA, then a presumptive drug-resistant therapy is recommended rather than the initial four-drug used in the USA which in turn, minimizes both mortality and costs [48].

In the selection of antimicrobials for the treatment of hospitalized severely ill patients, institutions generally cannot not apply fixed threshold criteria for guiding therapy decisions. Rather many clinicians and policy makers will review resistance rates among the agents available in their setting, and choose among the one, two, or three agents with the lowest rates of resistance when treating the severely ill. If resistance rates are above arbitrary thresholds for the most important pathogens, for example 5%, 10%, or 20%, clinicians and public health officials should be particularly attentive to the important of monitoring treatment failures and the potential need to revise formularies and treatment recommendations.

For the treatment of some non-life-threatening conditions in relatively healthy individuals, much higher rates of resistance to first-line agents may still be compatible with an overall acceptable level of health outcomes. Unfortunately, what is considered "acceptable" in terms of rates of resistance, treatment failure, and relapses will need to be balanced against what is achievable with the resources available.

In the absence of stronger data, policy makers may wish to establish a series of arbitrary thresholds for resistance estimates which should trigger formal review of treatment recommendations, for example: zero to non-zero percent (first emergence of resistance), 5%, 10%, 20%. The review may be as simple as a meeting to discuss the disease characteristics (causative organisms, trends of resistance in first-line and alternative agents, and subjective perceptions of clinical outcomes) and drug management issues (cost implications of a switch, number of available alternatives, desire to withhold use of "reserve" agents). Alternatively, the review may include more extensive evaluations of therapeutic alternatives.

If more than one organism is a common etiology for a specific clinical syndrome, the relative frequency of each organism should be considered when

establishing thresholds. For example, both *S. pneumoniae* and *H. influenzae* are common causes of respiratory disease and meningitis. For a specific geographic area, if *S. pneumoniae* is much more common than *H. influenzae*, then accepting higher thresholds of resistance in the latter may still be compatible with an overall satisfactory level of clinical outcome in empirically treated patients. Similarly, choroquine is still a valuable antimicrobial for the treatment of malaria in many countries despite widespread resistance to it in *P. falciparum* as the majority of patients with malaria may have non-falciparum strains.

## *6. 3. Clinical surveys -- monitoring of treatment outcome*

Another method for validating the appropriateness of STGs is the monitoring of patient outcomes, for example clinical improvement or cure, length of illness, volume of diarrhea, blood hemoglobin, relapse, frequency of complications, death. Such "*in vivo*" studies may be expensive and labor-intensive, thus are usually not appropriate for ongoing use. But an important characteristic is their relevance to direct and meaningful assessments of health system performance. There are many factors besides resistance which can lead to poor outcomes. Thus in the absence of additional information -- such as accuracy of diagnosis, level of clinician and patient compliance with STG recommendations, quality of administered drug -- a high rate of clinical failures may not necessarily call for a change in first-line agents. When complemented with laboratory testing, *in vivo* studies can permit a direct correlation between resistance findings and clinical consequences.

High rates of treatment failure undermine patients' confidence in the health care system, encourage self-medication, and promote "shopping" between health care providers. Patients fail therapy for a number of reasons besides infection with antimicrobial-resistant microbes. An understanding of the relative contribution of these various factors to failure rates can help national authorities target appropriate interventions to improve treatment success.

1. <u>Health care provider</u>

   *Causes of treatment failure*: incorrect diagnosis; incorrect prescription; incomplete therapy, for example treating bacterial dysentery without oral rehydration therapy or abscesses without surgical drainage. Problems may be due to poor compliance with existing STGs or alternatively to the use of inappropriate STGs.

   *Corrective Strategies*: reevaluate the recommendations in current STGs and modify them if necessary; improve compliance with existing STGs through education and managerial interventions.

2. <u>Patient</u>

*Causes of treatment failure*: severity of illness, underlying conditions (AIDS, malnutrition, *etc.*); poor compliance with treatment.

*Corrective strategies*: improve health facility capacity for managing severely ill or complicated patients, including mechanisms for referring and transferring patients; improve patient compliance with treatment instructions through education, directly-observed therapy, single-dose therapy, or other intervention [49, 52, 53].

3. Drugs

*Causes of treatment failure*: lack of access to prescribed medicines, poor drug quality, drug interactions.

*Corrective strategies*: improve procedures for drug management, ordering, procurement, distribution, and storage; ensure adequate quality of provided medicines.

4. Pathogen

*Causes of treatment failure*: resistance to the recommended antimicrobial, correct clinical diagnosis by the physician (for example pneumonia) but with an unexpected or infrequent species (fungal pneumonia).

*Strategy*: improve diagnostic laboratory capabilities; define criteria for laboratory testing; if necessary change treatment recommendations in the STG to better reflect local resistance issues.

At present, most treatment decisions throughout the world are made empirically. Unfortunately, there are a number of pressing demographic changes in patient populations which are significantly compromising the utility of syndrome management: rises in the numbers of HIV-infected and malnourished individuals, elderly patients with chronic underlying conditions (diabetes, immobility in long-term care institutions), patients with medically-induced immunocompromised (chemotherapy, steroid treatment), and increasing rates of antimicrobial-resistant organisms. Public health authorities must thus recognize the growing importance of laboratory diagnostic support in ensuring satisfactory clinical outcomes.

Methodologies for adapting treatment guidelines in view of resistance issues using clinical outcome measures have been most thoroughly developed and validated for the management of malaria [54-58] and tuberculosis [48].

Clinical efficacy studies: For a new antimicrobial to be introduced onto the market, a manufacturer must present data documenting the efficacy of the compound in achieving treatment objectives in a high proportion of treated individuals. Within the context of a clinical trial, this is generally in comparison to an alternative agent or to a placebo control. In the absence of a control, comparisons can still be made against historical rates of treatment success or to a defined level of performance acceptable.

Periodic efficacy studies have been integrated into a number of national malaria control programs. Examples of recommendations for the treatment of *P. falciparum* for specific geographic and demographic patient populations include: 1) if treatment with the first-line agent results in 25-35% treatment failures, switch to an alternative [59]; 2) if RIII resistance (*i.e.* high-level resistance defined on clinical criteria) to chloroquine is greater than 14-31% in young children, switch to an Fansidar [60]; and 3) if RIII resistance is 5-10%, evaluate the clinical and hematological outcome of each patient at 14 days. If symptoms persist or if there insufficient evidence of hematological recovery, switch to a second-line agent [57, 58].

Lot quality assurance: Lot quality assurance is a technique developed in manufacturing industries for the ongoing monitoring of the quality of supplies, components, and products. As it has been applied to malaria therapy decisions [61] a "defect" is a treatment failure. An acceptable overall level of treatment failure is defined, for example 5%. In a particular series of treated patients, failure rates may be somewhat higher than this, for example 6%, yet still considered to be "close enough" to 5% so as not to trigger an alarm. Lot quality assurance methods permit the calculation of a treatment failure threshold in a series of patients, for example 7%, beyond which investigative or corrective actions should be undertaken, for example review of drug quality and compliance with treatment protocols, determination of *in vitro* resistance rates, or a formal clinical efficacy study, as described above.

Lot quality assurance strategies have been successfully used as a rapid field tool for flagging potential problems that require more thorough investigations, but should not be used in isolation to modify treatment recommendations. Lot quality assurance methods can be applied to conditions other than malaria as part of an ongoing evaluation of the successful implementation of treatment guidelines (drug availability, quality, compliance, *etc.*). However, the availability of inexpensive laboratory test methods for resistance for common bacterial microbes decreases the relative value of lot quality methods in guiding antimicrobial selection recommendations.

## *Decision analysis*

A number of decision analysis techniques have been developed which permit more quantitative and explicit expressions of factors which impact health outcomes [62] [63]. Well-designed studies with relevant parameter estimates can provide meaningful estimates of the clinical (treatment outcome measures), financial (direct and indirect costs to the health care system and to the patient), and public health (disease prevalence, resistance selection, transmission) impacts of different policy decisions and highlight those decision nodes and variables of greatest import.

Unfortunately, 1) many models and studies do not adequately capture the complex realities of the disease epidemiology and the decision-making process; 2) as developed to date, decision analysis methods focus on short-term outcomes measures (health outcome, costs), and thus do not consider implications for the development of resistance over time, particularly against reserve agents; and 3) the required parameters and estimates for models are often unavailable, unreliable, or inappropriate for the studied population. To address uncertainties in the model parameters, sensitivity analysis is often appropriate to explore the robustness of conclusions under a variety of assumptions and values for parameter estimates

Cost effectiveness analyses: A number of studies have estimated the financial and health outcome implications of therapy alternatives [63] [64-66]. Costs include not only the costs for medications, but generally include the costs associated with the management of treatment failures, hospitalization and personnel costs, patient outlays, and diagnostic testing. Therapy alternatives may be compared on the basis of average cost per patient treated, cost per year of life saved, or cost per DALY (disability-adjusted life years). Cost effectiveness methods have been usefully applied in studies of malaria [67]; [60] tuberculosis [48, 68-70] [71] urinary tract infection [72-77], Otitis media [78] chronic bronchitis [79] community-acquired pneumonia [72, 80], gonorrhea [81] HIV/AIDS [4, 82] and bovine respiratory illness [83]. In several of these studies, resistance alert thresholds for switching first-line therapy for the clinical and geographic setting considered are proposed.

Clinical decision trees: Ultimate therapy outcome in an individual patient is viewed as a tree of branching decisions (for example, use of antimicrobial 1, antimicrobial 2, no therapy) and intermediate outcomes (response to initial therapy, subsequent relapse, response to second-line therapy). Branches at each node of this tree are associated with a probability directing the course of the patient's illness (resistance rates, rates of treatment failure in the presence of resistance, rates of relapse). Treatments outcome may include complete no improvement,

recovery, recovery with disability, or death, each of which is assessed a "utility" between 0 and 1. Death is assigned a utility of 0, complete recovery has a utility of 1, and other possible outcomes are assigned subjective intermediate utilities. It is possible to calculate for each therapy branch an overall utility. Comparison of the utilities of the various therapeutic options will suggest which agent would provide the best average utility in terms of health outcomes. For each probability, a range of estimates can be entered, permitting a sensitivity analysis of the robustness of conclusions.

Besides measures of health "utility", additional analyses may address concerns of importance, for example financial costs and rates of death and disability associated with each therapy option. Conclusions from these alternative approaches may support or conflict with the recommendations obtained strictly on the basis of health utility measures. Applications of clinical decisions trees addressing antimicrobial resistance have been described for urinary tract infections [76] and community-acquired pneumoniae [84].

Disease simulation models: Researchers have developed mathematical approaches for modeling trends in resistance prevalence for microorganisms in a number of settings, such as laboratory experiments, hospital wards, small communities, and countries [85, 86] [87-89]. Other studies, for example those used in guiding recommendations for antiretroviral therapy strategies [90-92] have used resistance rates and rates of resistance emergence in models of disease transmission, permitting an evaluation of the impact of different therapy options on disease prevalence, treatment success rates, and costs.

## *Antimicrobial recommendations in outbreaks: preparedness and response*

Outbreaks due to multiresistant organisms such as *Shigella*, *Salmonella* Typhi, and *M. tuberculosis* have been associated with higher rates of morbidity and mortality than those associated with susceptible strains. Thus in responding to local outbreaks or national epidemics, early identification and investigation are critical in developing treatment and containment strategies.

In preparation for and in the early stages of an epidemic, recommended therapy should be guided by knowledge of baseline resistance trends in the area and of the clinical relevance of resistance, as described earlier. However, for epidemic-prone species, there should be an additional awareness of the threat posed to epidemic containment strategies if ineffective antimicrobials are prescribed. Consequently, therapy recommended for use early in an

epidemic situation may be geared towards the more expensive and effective reserve agents.

With early laboratory investigation of clinical isolates, laboratory testing may suggest that a single epidemic strain is responsible. In such an instance, antimicrobial therapy may be targeted against this single strain, for example with the cheapest, safest, and most convenient antimicrobial found to be effective in laboratory testing of representative isolates. If multiple strains are identified, then overall prevalence of resistance will need to be ascertained prior to selection of an antimicrobial.

## *Monitoring*

Methodologies for monitoring clinical efficacy are discussed in Section 6.3 *Clinical surveys -- monitoring of treatment outcomes*. Monitoring programs may focus specifically on the issue of treatment failure or alternatively may be integrated into more complete disease and resistance surveillance programs. Findings of unacceptably high rates of treatment failure should prompt a thorough investigation and evaluation of the factors mentioned above. For example, are there problems in the treatment guidelines or in the implementation of the treatment guidelines? Are diagnoses correct? Are drugs of good quality available and used properly by patients? Investigations should document clinical failures rates, physician compliance with STGs, patient compliance with prescriptions, drug quality, and antimicrobial resistance estimates. High rates of clinical failure despite good compliance with STGs should prompt an immediate review of official recommendations.

In several countries, formal treatment failure monitoring programs have been established for the following clinical outcomes in patients with certain conditions such as malaria [54, 67, 93] and tuberculosis [5] and findings have been used in been used in adjusting therapy guidelines. For most infectious diseases, however, ongoing systems for formal monitoring of clinical outcome are usually not in place. Unfortunately in practice, such systems would most likely prove unwieldy, inaccurate, incomplete, and time-consuming. However, at a minimum there should be mechanisms by which: 1. health care providers can express their concern or perception to the relevant policy-making bodies that clinical success may perhaps be inadequate for certain clinical scenarios covered by STGs; and 2. national authorities in collaboration with researchers and clinical societies can respond to identified concerns with formal studies or informal investigations.

## 9. SOURCES OF DECISION-SUPPORT INFORMATION

### 9.1 Need to understand and integrate other types of decision support information

The flow of in-country data on antimicrobial resistance, sketched above, needs ongoing interpretation in the context of other general types of decision-support information. Surveillance studies of resistance prevalence in other parts of the world frame evaluation of data produced in any country. Clinical trials report how often various antimicrobial agents improve survival or shorten the duration of infections due to many kinds of microorganisms, and to what extent various levels of resistance diminish these effects. Recent publications from India, for example, report that strains of *Salmonella typhi* found to have a single-step mutation that raises resistance to fluoroquinolones only slightly, to a level still categorized as susceptible, respond more slowly to treatment with such agents.

Antimicrobial resistance is in itself a complex subject. Resistances to different antimicrobial agents in different kinds of bacteria vary greatly in their genetic vectors, mechanism of action and epidemiology, some of which affect use of the agents. So also do variations in the pharmacology of the agents and in the ways in which different kinds of bacteria infect. A level of expertise for interpreting information in these areas, perhaps boosted by special training, may have to come from different participants in the CQI process e.g. microbiologist for understanding of resistance, pharmacologist for agent pharmacology and clinician for treatment, and specialist discussers from outside the country as needed.

While harder to organize and measure, a major source of decision-support information for antimicrobial choice in any country is the experience of its caregivers making those choices at all levels. They are in the best position to discriminate among patients grouped into one syndromic diagnosis subgroups of patients with differing clinical presentations that may correspond to infection with different types of microorganisms, e.g. *shigella* or *cholera*. Noticing a shift in prevalence of patients within such "clinical impression" subcategories of one syndromic diagnosis may trigger recognition of an impending outbreak and reveal implications for both treatment and public health. Caregivers also need to be sensitive detectors of treatment failure and of early shifts in prevalence of treatment failure, which can be critical information for decision-support.

Special effort or systems are needed to fully utilize the experience of caregivers, who may feel that information flows from top down and so underestimate the value of their aggregated observations. To aggregate caregiver input systematically, information systems for decision-support can develop ways to elicit it and forms and fields to accept and analyze it. Doing this closer to real time, and initially in selected sets of caregivers, could

trigger special arrangements to send to a distant laboratory a culture of an index or near-index case suspected to be of special significance. This would have potential for early detection of, and for triggering public health or therapy-altering responses to, new outbreaks, shifts in prevalence of the kinds of microorganisms causing a syndromic diagnosis or shifts in prevalence of resistance in one kind of bacteria.

## 9.2 Variations in the emergence, spread and linkage of antimicrobial resistance

Understanding of the nature of antimicrobial resistance is another essential component of antimicrobial decision support. It can help us not only to anticipate and circumvent resistance in treating any patient but also to avoid making it worse for future patients.

When each antimicrobial agent was first introduced it could usually kill all known strains of the kinds of bacteria that were its intended targets. After each agent became widely used, however, strains of such bacteria resistant to it eventually emerged and spread.
Resistance to some agents emerges often. Resistance to naladixic acid or to rifampicin can arise from a single mutation occurring as often as in one in ten million bacteria, a tiny fraction of what each of us carries. In contrast, resistance to vancomycin or the kind of resistance to penicillin that is seen in *Streptococcus pneumoniae* required the ultimate improbable assembly somewhere of very specific genetic elements of diverse origins and so first emerged only after those agents had been used widely for many decades..

For these reasons, the propensity of any antimicrobial agent to promote resistance may differ greatly with the agent and with time and place. Each use of an agent that elicits resistance frequently carries from the beginning a high risk of eliciting a new emergence, and after there have been many such emergences an additional risk of spreading one of the increasingly ubiquitous emerged clones. Conversely, each use of the more numerous agents to which resistance emerges only rarely carries initially only a miniscule risk of eliciting that rare emergence event, and then even after it happens somewhere else, may not for a long time encounter and spread any of the emerged strains resistant descendants. By the time it does arrive, however, the slow-to-emerge resistant gene may have evolved in its long passage

Use of an agent that elicits resistance frequently would cause that resistance to emerge often and in many places. Such ubiquitous origins may make prevalence of the resistance more uniform over wide areas. Conversely, resistance that emerges only very rarely may eventually spread far only in the descendents, the clone, of a rare emerged strain or in clones of genetic elements transferred from it. Spread of such resistance predominantly in one

or a few bacterial or genetic-vector clones, even if ultimately global, may be erratic, making its distribution uneven for long periods.

# 10. Developing Standard Treatment Guidelines for priority bacterial diseases

Section 1 *Standard Treatment Guidelines and surveillance of antimicrobial resistance* presented a number of principles and strategies for addressing antimicrobial resistance in the development of STGs. The purpose of this chapter is to provide more detailed guidance in the adaptation of STGs for specific diseases and clinical syndromes in light of currently recognized issues in resistance. The discussion will focus on those issues most directly related to the selection of antimicrobials for STGs. For further details on other clinical, therapeutic, and epidemiological aspects, the reader should consult other references [1] [3, 43, 44].

## 10.1 Acute gastroenteritis

### *Etiology*

A leading cause of infant and childhood mortality, acute gastroenteritis is a syndrome, most frequently characterized by diarrhea, caused by a diverse variety of bacterial, viral, and parasitic pathogens as well as by a number of non-infectious causes. As depicted in Table 1, an important and useful distinction can be made between watery diarrhea, which tends to be a noninflammatory, secretory condition of the small intestine, and dysentery, an invasive disorder of the large intestine. The most important bacterial pathogens include pathogenic *E. coli*, *Salmonella* spp., *Campylobacter jejuni*, and in some countries *Shigella* spp. and *Vibrio cholerae*.

Diarrhea in individuals with the HIV virus is an important issue in the development of STGs for populations with high rates of infection. In addition to the organisms causing diarrhea in patients with intact immune systems, a number of additional infectious and non-infectious etiologies must be considered. In addition to the pathogens common among non-HIV infected individuals, etiologies include cytomegalovirus, *Cryptosporidium* spp., *Microsporidium* spp., *Isospora belli*, and *Mycobacteria* spp. For patients with persistent and debilitating diarrhea, laboratory diagnostic support is often required to guide therapy decisions.

### *Therapy*

While the clinical distinction between watery and invasive diarrhea is frequently not clear-cut, the mainstay of therapy in all instances remains fluids, particularly the use of oral rehydration therapy (ORT). The use of antimicrobials should be viewed principally as a secondary treatment option for

a defined subset of patients, for example patients with severe dehydration, septicemia, or underlying disorders such as immunocompromise, sickle cell disease, or severe malnutrition. Objectives of antimicrobial therapy include shortening the duration of disease, decreasing the volume of diarrhea, preventing severe complications and death, and lowering the risk of spread to other individuals. Some examples of recommendations for therapy are presented in Table 1. Thorough discussions of the value and selection of antimicrobials in the management of diarrhea are available from guidelines of the Infectious Diseases Society of America [3], and a number of scientific and review articles [94-98].

It should be stressed that for several of organisms, antimicrobials have proven of no or limited value in improving patient outcomes. There are even suggestions that antimicrobials can occasionally worsen a patient's condition (*e.g.* increased toxin production in enterohemorrhagic *E. coli*) or increase the risk of prolonged excretion (*e.g.* nontyphoidal *Salmonella*). Antimicrobial therapy is only indicated routinely in the treatment of a few species, such as *Shigella* spp., *Vibrio cholerae*, and *Entamoeba histolytica*. For species such as *Campylobacter* and non-typhoid *Salmonella*, antimicrobials are usually reserved for patients with more severe disease.

Patient management is generally empiric, *i.e.* without supportive laboratory tests. In the absence of knowledge of the specific etiologic agent, the clinician or policy maker must assess the likelihood of infection with various organisms in the patient's epidemiological setting, rates of antimicrobial resistance, and the possible consequences of non-use of an antimicrobial or the use of an antimicrobial ineffective for the infecting organism. It is important to have a sense as to the relative frequency of various organisms -- bacterial, viral, parasitic -- causing diarrhea in the local setting. If *Shigella* spp. are common, antimicrobials selected for inclusion in the STG should reflect to a greater extent resistance in *Shigella*. If a high proportion of cases are due to intestinal parasites, the STG may recommend the use of microscopy for detection of ova and parasites.

## *Resistance issues*

As the mainstay of therapy is fluids, resistance is not an important clinical concern in the management of most patients. Consideration of resistance issues is only a priority for a few species of public health importance.

For several of the organisms listed, fluoroquinolones are recommended. They are generally safe, easy to administer compounds which are highly effective against most bacterial causes of diarrhea. However, fluoroquinolones are often expensive, resistance is rising rapidly for some pathogens, and they are commonly used as reserve agents for the treatment of the severely ill.

Consequently, prudent use of this class of drugs is to be strongly advised. It should be noted fluoroquinolones have not been approved by several regulatory agencies for use in children or in pregnant women, so use of an alternative agent may be recommended in these groups. On the other hand, several studies have suggested that single-dose and short-course therapy is safe in pediatric populations [99-101].

Water diarrhea

*V. cholerae*: Cholera is a self-limited disease requiring usually no more than therapy replacement, though often in massive amounts. To decrease the length of illness, volume of diarrhea, and risk of transmission to others, antimicrobial therapy of recognized or suspected cases of cholera is generally recommended. Inexpensive antimicrobials commonly prescribed include tetracycline, doxycycline, ciprofloxacin, ampicillin, erythromycin, and co-trimoxazole (trimethoprim/sulfamethoxazole). Other options include chloramphenicol and furazolidone. Resistance rates vary widely by region and from outbreak to outbreak. Resistance to co-trimoxazole is widespread, while resistance to ampicillin, tetracycline, and doxycycline is common in some areas. In epidemics, early investigation of the resistance characteristics of the outbreak strain should be instituted.

Enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC): Most commonly associated with childhood diarrhea in developing countries and in traveler's diarrhea, treatment is principally supportive. For the treatment of severe dehydration or to decrease the length of illness in milder disease, antimicrobials found to be of value include co-trimoxazole, ampicillin, tetracycline, doxycycline, and fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin). Resistance to the first three of these agents has been identified worldwide and is rising. Fluoroquinolone resistance, including that mediated by transferable plasmids, has been identified, but to date remains infrequent.

Nontyphoidal *Salmonella* spp.: Therapy of mild-to-moderate cases of *Salmonella* enteritis has not been shown to provide any clinical benefit. For severe cases and in patients with high risk of invasive disease, antimicrobials commonly prescribed include ampicillin, fluoroquinolones, co-trimoxazole, and third-generation cephalosporins. Other agents which have been used include tetracycline and chloramphenicol. Resistance is more common in some serotypes of *Salmonella* (such as *S.* Typhimurium, *S.* Newport, *S.* Dublin, *S.* Wien) than in others (such as *S.* Enteritidis). Resistance to all of these agents has been identified. The recent identification and rises in resistance to

fluoroquinolones and third-generation cephalosporins are particular concerns.

Dysentery

*Shigella*: Most mild-to-moderate cases of *Shigella* will resolve in the absence of antimicrobial therapy. However, given the risk of life-threatening complications and transmission to others, therapy of recognized or suspected *Shigella* is usually indicated [102]. For years, antimicrobials effective in shigellosis included ampicillin, tetracyclines, sulfonamides, and co-trimoxazole, amdinocillin, furazolidone, and nalidixic acid. Unfortunately, resistance to each of these agents has emerged and in many parts of the world, resistance levels are high. *Shigella dysenteriae* type 1, the strain most frequently identified with large outbreaks and with high mortality rates, has been particularly adept at acquiring resistance. Failure rates are high when strains are treated with an antimicrobial without *in* vitro activity. Fluoroquinolones (ciprofloxacin, norfloxacin, levofloxacin) are highly effective against *Shigella* isolates, though resistance is increasing and is a significant concern, particularly given the absence of obvious therapeutic alternatives. Results with third-generation cephalosporins and azithromycin are encouraging. Nalidixic acid is generally effective against susceptible isolates of *Shigella*, but resistance has risen rapidly and is often associated with decreased susceptibility to fluoroquinolones.

In epidemics of shigellosis, clinical isolates are usually found to share resistance characteristics. In this scenario, therapy should be directed towards those compounds found to be effective against the outbreak strain or strains.

*Campylobacter*: The antimicrobials most commonly used in the treatment of moderate-to-severe cases of *Campylobacter* enteritis and in patients at high risk for complications are the macrolides (erythromycin, azithromycin) and fluoroquinolones (ciprofloxacin, norfloxacin). Other antimicrobials with activity against *Campylobacter* include tetracyclines, amoxicillin, ticarcillin/clavulanic acid, aminoglycosides, chloramphenicol, clindamycin, and nitrofurans. Resistance to macrolides and fluoroquinolones has increased rapidly over the past decade, and has been correlated to the use of fluoroquinolones in the poultry industry.

Nontyphoidal *Salmonella* spp.: See the discussion above of resistance in *Salmonella* spp. under watery diarrhea.

Enterohemorrhagic *E. coli* (EHEC): Several studies have suggested that treatment of patients with EHEC can worsen the disease and precipitate hemolytic uremic syndrome (HUS). Thus in patients suspected to have EHEC on the basis of laboratory findings or within the context of a recognized outbreak, antimicrobials are not indicated.

Enteroinvasive *E. coli* (EIEC): EIEC causes a clinical syndrome similar to shigellosis. Therapy with antimicrobials, such as ampicillin the co-trimoxazole, may be effective, though in many parts of the world, resistance is common. Fluoroquinolones are usually effective. Resistance has been identified but remains low.

*Yersinia enterocolitica*: Diarrhea caused by *Y. enterocolitica* is generally self-limited, not requiring antimicrobial therapy, and is relatively infrequent in most parts of the world. For invasive infections and more severe disease, aminoglycosides, chloramphenicol, tetracycline, doxycycline, co-trimoxazole, and ciprofloxacin. Resistance to these agents has not been a significant public health concern.

*Clostridium difficile*: Necrotizing entercolitis, or pseudomembranous colitis, caused by *C. difficile* may be seen as a complication of antimicrobial therapy, most frequently in hospitalized patients. Withdrawal of the causative antimicrobial may be sufficient for management of mild cases. For more severe cases, oral metronidazole or vancomycin may be used. The former is usually preferred due to its lower cost and narrower spectrum of activity. Resistance to these two agents has not been identified. Other agents which may be considered include teicoplanin, fusidic acid, and bacitracin, though the latter two are associated with higher rates of relapse.

Table 1. Etiologies of acute gastroenteritis, recommendations for therapy, and priorities in resistance ([1, 43]. An entry of "Severe cases" with antimicrobial options and resistance concerns appearing in italicized parentheses indicates that antimicrobials are not indicated in most patients with mild-to-moderate disease. Antimicrobials should be reserved for those patients with severe disease (such as advanced dehydration, invasive disease, bacteremia) or in patients at high risk of complications (elderly, patients with immunocompromise, malnourished, *etc*.).

AG = aminoglycoside, FQ = fluoroquinolone, 3GC = third-generation cephalosporin, AMP = ampicillin, AZI = azithromycin, CIP = ciprofloxacin, DOX = doxycycline, ERY = erythromycin, GEN = gentamicin, NAL = nalidixic acid, TET = tetracycline, SXT = co-trimoxazole (trimethoprim/sulfamethoxole), VAN = vancomycin

| Organism | Antimicrobial Therapy? | Some antimicrobial options | Important Resistance? |
|---|---|---|---|
| **Water diarrhea** | | | |
| ***Bacterial*** | | | |
| Enteropathogenic *E. coli* (EPEC) | Severe cases | *(SXT, DOX, FQ, AMP)* | *(Yes)* |

| | | | |
|---|---|---|---|
| Enterotoxigenic *E. coli* (ETEC) | Severe cases | *(SXT, DOX, FQ, AMP)* | *(Yes)* |
| *Salmonella* spp. (nontyphoidal) | Severe cases | *(AMP, FQ, SXT, 3GC)* | *(Yes)* |
| *Vibrio cholerae* | Yes | DOX, TET, FQ, ERY, AMP, SXT | Yes |
| ***Other*** | | | |
| Rotavirus, other enteric viruses | No | None | No |
| *Cryptosporidium* spp. | Severe cases | Paromomycin | No |
| *Giardia lamblia* | Yes | Metronidazole, tinidazole | No |
| **Dysentery** | | | |
| ***Bacterial*** | | | |
| *Campylobacter jejuni* | Severe cases | *(ERY, AZI, FQ, TET, GEN)* | *(Yes)* |
| *Clostridium difficile* | Yes | Metronidazole, VAN | No |
| Enterohemorrhagic *E. coli* (EHEC) | No | None | No |
| Enteroinvasive *E. coli* (EIEC) | Severe cases | *(SXT, DOX, FQ, AMP)* | *(Yes)* |
| Nontyphoidal *Salmonella* spp. | Severe cases | *(AMP, FQ, SXT, 3GC)* | *(Yes)* |
| *Shigella* spp. | Yes | CIP, NAL, AMP, SXT, TET, CHL | Yes |
| *Yersinia enterocolitica* | Severe cases | *(AG, CHL, DOX, SXT, FQ)* | No |
| ***Other*** | | | |
| *Entamoeba histolytica* | Yes | Metronidazole+other agent | No |

## *Surveillance priorities*

In the development of STGs for management of diarrhea, surveillance of the following issues should be considered priority:

1. Proportion of various pathogens: Committees responsible for developing STGs for diarrhea must have a sense of the relative frequency of the various bacterial, viral, and parasitic organisms causing diarrhea in the local clinical setting. Data should highlight the proportion of cases in which antimicrobial therapy of some sort may be indicated. Therapy recommendations should be geared towards those organisms found to be most prevalent, cause the greatest morbidity, and are of greatest public health concern.

2. Shigella spp. (in countries in which *Shigella* is common): Surveillance should be conducted with the traditional first-line agents such as ampicillin, chloramphenicol, co-trimoxazole, tetracyclines, and nalidixic acid, as these compounds do remain highly active against susceptible strains. Surveillance for resistance to ciprofloxacin is also a public health priority. In the setting of a shigellosis outbreak, prompt efforts must be made early to characterize the resistance phenotype of the outbreak strain.

3. Vibrio cholerae (in countries in which cholera is common): Surveillance of the drugs most commonly used in treating cholera in the country, for example tetracycline, doxycycline, ciprofloxacin, ampicillin, erythromycin, and co-trimoxazole is recommended. Quinolone resistance at present is rare, so findings of any resistant strains should considered to be of international public health importance.

Countries with additional resources may wish to consider surveillance of the following organisms and antimicrobials. Antimicrobials are usually unnecessary except in patients with severe illness or conditions which may predispose to a poor clinical outcome. For those patients warranting treatment with antimicrobials, clinically importance resistance to traditional first-line agents has been identified, so surveillance of isolates may prove helpful in the development of STGs.

4. Nontyphoidal *Salmonella* spp.: For the clinical management of patients with severe disease or risk factors for complications, surveillance of resistance to ampicillin, a fluoroquinolone, and a third-generation cephalosporin is recommended. For epidemiological purposes, the inclusion of a number of additional agents, such as chloramphenicol, tetracycline, sulfamethoxazole, and aminoglycosides, may be of value. It should be noted that aminoglycosides and first- or second-generation cephalosporins have little benefit clinically, despite susceptible results in *in vitro* testing.

5. *Campylobacter jejuni*: Surveillance of resistance to macrolides, such as erythromycin and azithromycin, and fluoroquinolones. *Campylobacter* is a fastidious organism which may be difficult to isolate and test by routine clinical laboratories. Guidelines for standardized susceptibility testing of *Campylobacter* isolates are currently under development by the U.S. National Committee for Clinical Laboratory Standards.

6. Pathogenic *E. coli*. The distinction between EPEC, ETEC, EHEC, and EIEC is generally only possible in specialty research and public health laboratories, and the principal modality of therapy is rehydration. Consequently routine surveillance of resistance in these organisms is not indicated, but may be of value in countries in which these organisms are common and in which resistance has found to be an important concern. As antimicrobial therapy is not indicated in the treatment of EHEC, surveillance of resistance for clinical purposes is not necessary.

## 10.2 Respiratory infections and meningitis

### *Etiology*

The organisms covered in this section cause a spectrum of conditions of the respiratory tract. This section will focus on agents causing pharyngitis, acute otitis media, and community-acquired pneumonia [6]. As a number of the organisms also cause meningitis with similar antimicrobial resistance concerns, meningitis is also presented here.

In developing STGs for respiratory infections and meningitis, a few key factors must be kept in mind. To a greater degree than many infectious diseases, the agents most frequently associated with these infections are greatly dependent on patient age reflecting changes in host immunity and exposures over time. Similarly, the availability and use of effective vaccines for certain organisms, for example *H. influenzae* Type B, S. *pneumoniae,* and *N. meningitidis*, may impact the relative frequency with which certain pathogens are isolated.

In populations in which infection with HIV is common, a number of additional etiologies and treatment issues must be considered. Laboratory support is often necessary for adequate management of these patients.

*Acute otitis media*: Acute otitis media is most common in young children, up to approximately 5 years of age. The most common bacterial agents are *Streptococcus pneumoniae, Haemophilus influenzae* (particularly non-invasive non-typable strains and occasionally invasive type B strains), and *Moraxella (Branhamella) catarrhalis*. Otitis media "with effusion" (*i.e*. with fluid accumulation but without evidence of pus and invasive disease) generally does not require the use of antimicrobials.

*Community-acquired pneumonia*: *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* are important causes of pneumonia at any age (*Staphylococcus aureus* may also be seen at any age, but to a much lower degree). Neonates are prone to infection by a number of additional agents not commonly found in older children, such as Group B streptococci, *Escherichia coli*, and other *Enterobacteriaceae*. For young children (ages 2 months to 5 years), important concerns besides the pneumococcus are *H. influenzae* (especially Type B) and respiratory viruses. Pneumococcal pneumonia and "atypical" pneumonia with *Mycoplasma pneumonia* and other distinctive pathogens are commonly observed in older children and adults. Aspiration pneumonia may be seen in debilitated or alcoholic patients. In patients with HIV/AIDS, additional pathogens to consider include *Pneumocystic carinii*, cytomegalovirus, *Cryptococcus neoformans*¸ and *Rhodococcus equi*.

*Other respiratory infections*:

- *Common cold*: Most non-specific upper respiratory infections, such as the common cold, are caused by respiratory viruses.

- *Pharyngitis*: Most cases of pharyngitis are due to respiratory viruses. Bacterial pharyngitis is most commonly caused by the streptococcal Group A organism *Streptococcus pyogenes*.

*Meningitis*: As is the case for pneumonia, *S. pneumoniae* is an important cause of meningitis at any age. In addition, newborns may exhibit meningitis caused by Group A and Group B streptococci, *E. coli*, *Listeria monocytogenes*, *Enterococcus* sp., among others. Besides the pneumococcus, *H. influenzae* Type B is a common cause of meningitis in non-vaccinated populations of children aged 2 months to 5 years. The most common causes of meningitis in adults are *S. pneumoniae* and *N. meningitidis*, with occasional infections with *Listeria monocytogenes* and *M. tuberculosis*. Viral meningitis can also occur at any age. Causative agents include enteroviruses, herpes viruses, and polio virus. In patients with HIV/AIDS, *Cryptococcus neoformans* and *M. tuberculosis* are important concerns.

## *Therapy*

Many of the infections cited above are due to respiratory viruses and require no more than supportive and symptomatic therapy with antipyretics, fluids, and perhaps decongestants and antihistamines. For respiratory illnesses caused by bacteria, many patients with an intact immune system will exhibit spontaneous recovery from infections such as pneumonia and otitis media, even in the absence of therapy. However, antimicrobials are still generally recommended in order to decrease the length of illness and to prevent short-term complications (respiratory failure, progression to septicemia and meningitis, death) and long-term sequelae (such as rheumatic heart disease after a case of streptococcal pharyngitis). Bacterial meningitis should always be treated urgently to prevent severe complications and death, as well as long-term complications, such as deafness.

*Acute otitis media*: Acute otitis media is most frequently a disease of young children [103]. Since the specific etiologic agent in a child is usually unknown, empiric therapy should be directed against the most frequent organisms implicated: *S. pneumoniae, H. influenzae,* and in some areas *M. (B.) catarrhalis*. Antimicrobials found to be useful include amoxicillin (usual or high doses), co-trimoxazole, amoxicillin/clavulanic acid, oral cephalosporins (cefaclor, cefuroxime axetil, *etc*.), and erythomycin/sulfisoxazole. Treatment failures are common in some children, so switching to an alternative agent should be considered if clinical recovery is not prompt.

*Community-acquired pneumonia*: Treatment of community-acquired pneumonia should be guided by the patient's age, clinical history,

disease severity, risk factors, and knowledge of the prevalence of various pathogens in the local setting [104]. Where feasible, Gram stain and X-ray results may be helpful. Further details on specific etiologic agents are presented under *Resistance issues*. The following recommendations are abstracted from the document *WHO Model Prescribing Information: Drugs used for bacterial infections*.

- Neonates: Amoxicillin+gentamicin may be given as first-line therapy, and cefotaxime or chloramphenicol as second-line.
- Young children (2 months-5 years): Mild cases of pneumonia can be treated with amoxicillin or co-trimoxazole. For more severe cases, intravenous penicillin, ceftriaxone, or chloramphenicol are recommended.
- Older children and adults (> 5 years): Mild to moderate disease can be treated effectively with oral amoxicillin, erythromycin, doxycycline, or co-trimoxazole. If an "atypical" pathogen is suspected, then an agent such as erythromycin should be added. For more severe cases of pneumonia, intravenous penicillin, ceftriaxone, or penicillin+gentamicin should be administered. For patients with risk factors for *S. aureus* pneumonia, cloxacillin, cefazolin, clindamycin, vancomycin, or cloxacillin+gentamicin have be found effective.
- Tuberculosis: For the management of patients with tuberculosis, policy makers should consult available resources on DOTS and DOTS-Plus [5, 49, 52, 105].

*Meningitis*: Decisions regarding the selection of antimicrobials for the treatment of meningitis are crucial to the success of treatment protocols. In contrast to the situation with many respiratory infections, few patients with meningitis will recover without prompt and effective therapy and the risk of rapid progression to death is high. Patient age, physical findings (such as petechiae in patients with meningococcal meningitis), and epidemiological context (for example during a recognized outbreak of meningococcal meningitis) can guide the clinician in selection of antimicrobial. Where available, a cerebrospinal fluid Gram stain can immediately target therapy against the presumed pathogen.

For the treatment of newborns with meningitis, the document *WHO Model Prescribing Information: Drugs used in bacterial infections* recommends ampicillin plus either gentamicin or cefotaxime, or alternatively penicillin plus gentamicin. For older children and adults, ceftriaxone, cefotaxime, or penicillin+chloramphenicol for empiric therapy are recommended. If over 10% of the strains of *S. pneumoniae* have intermediate susceptibility to penicillin, then penicillin should not be used.

On the basis of a Gram stain, clinical findings, or occurrence during an outbreak, it may be possible to make a presumptive identification of the causative organism. Local estimates of resistance to these organisms can guide appropriate antimicrobial selection. The following organism-specific recommendations are possible:

-- *Streptococcus pneumoniae*. For penicillin-susceptible pneumococci, penicillin or third-generation cephalosporin are the drugs of choice. For penicillin intermediate strains, ceftriaxone may be effective. If strains resistant to penicillin or ceftriaxone are common, then a combination of vancomycin, ceftriaxone, and rifampicin is recommended, and referral of patients with resistant strains to a specialist.

-- *Haemophilus influenzae*: Ampicillin and chloramphenicol are effective against susceptible strains. For resistant strains, ceftriaxone is recommended. Prophylaxis of close contacts and family members with rifampicin, particularly those under 5 years of age should be considered. In children, encapsulated Type B strains are common causes of invasive disease. In adults, non-encapsulated strains are more common.

– *Neisseria meningitidis*: Treatment with penicillin or penicillin+chloramphenicol is recommended. Rifampicin or ciprofloxacin may be used for the prophylaxis of close patient contacts. Other agents active against *N. meningitidis* include third-generation cephalosporins, chloramphenicol, and fluoroquinolones.

*Other respiratory infections*: Antimicrobial selection for other respiratory infections is less problematic than for otitis media and pneumonia as either no antimicrobial is indicated or resistance has not yet been identified as an important public health concern.

-- *Common cold*: No antimicrobials are indicated.

-- *Pharyngitis*: For viral pharyngitis, no antimicrobial is warranted. For streptococcal pharyngitis, the treatment of choice is penicillin. For penicillin-allergic patients, a macrolide such as erythromycin may be used. In addition to a prompt recovery, an important objective of therapy for pharyngitis with *S. pyogenes* is prevention of rheumatic heart disease as a long-term complication.

## *Resistance issues*

For patients with meningitis, resistance is clearly an important public health concern which needs to be addressed in treatment guidelines. For the treatment of otitis media and pneumonia, the situation is more complex: eventual spontaneous resolution of mild to moderate disease may be seen without therapy; laboratory findings of resistance do not necessarily predict a poor clinical outcome, particularly if high-dose therapy is used; and some studies have suggested that the best predictors of poor response to therapy are indicators of disease severity (for example in pneumonia, radiological findings or blood cultures documenting bacteremia [106] rather than findings of resistance to the antimicrobial used for treatment. The establishment of resistance alert thresholds, including references for applications in respiratory diseases, were presented in Section 5 *Use of resistance data to guide therapy recommendations*.

*Streptococcus pneumoniae*: Resistance to a number of antimicrobials is common and increasing [107]. This is particularly a concern for the treatment of meningitis, but treatment failures in respiratory infections have also been identified. Several studies have suggested that resistance rates in invasive strains (blood and CSF isolates) tend to be lower than in non-invasive strains, and that resistance in children is often higher than in adults. Certain serotypes and clones of pneumococci have been particularly associated with multiple resistance as well as with greater virulence, an important consideration in the development and introduction of new vaccines.

-- *Beta-lactam antimicrobials*. For many decades, penicillin remained the drug of choice for this organism, but since the 1970s, changes in the organism penicillin-binding proteins (PBPs) have compromised the efficacy of this agent. Some modifications are associated with "intermediate-level" resistance, while others are associated with "high-level" resistance. Beta-lactam agents should not be used in patients with meningitis with strains that are not fully susceptible, as the risk of treatment failure is high. For respiratory infections on the other hand, therapy is often successful, despite laboratory findings of resistance, though higher doses of drug may be prudent. In the case of poor clinical response, therapy should be switched to a second-line agent.

- *Macrolides*. Macrolides such as erythromycin are frequently prescribed for patients with respiratory infections because of their coverage of "atypical" respiratory pathogens such as *Mycoplasma pneumoniae*, their cost and ease of administration, and value in penicillin-allergic patients. Resistance to macrolides has been associated with higher rates of treatment failure in

patients treated with macrolides. Macrolides are not indicated for the treatment of meningitis.

-- *Co-trimoxazole (trimethoprim/sulfamethoxazole)*. Resistance to this agent is common and rising. Nevertheless, this compound is commonly used to treat pneumonia. Some studies have suggested that patients infected with resistant strains do respond to therapy with co-trimoxazole, but the issue has not been thoroughly investigated. Co-trimoxazole is usually not used in cases of meningitis.

-- *Fluoroquinolones*. In developed countries, fluoroquinolones are widely used to treat mild-to-severe respiratory tract infections. *In vitro* resistance has been identified and is rising. Given their expense, their value in the treatment of several conditions, and the efficacy of cheaper agents (despite laboratory findings of resistance), fluoroquinolones are generally not recommended for use in the treatment of respiratory infections in low-resource countries.

-- *Vancomycin*. Resistance to vancomyin has not been identified in clinical isolates of *S. pneumoniae*. Though an expensive agent, vancomycin, in combination with other agents, is recommended as first-line therapy of meningitis in countries in which resistance to penicillin and third-generation cephalosporins is high.

*Haemophilus influenzae*: Resistance to the traditional first-line agents has been recognized [107] and is an important cause of treatment failure in cases of meningitis. The clinical relevance of resistance in the treatment of pneumonia is less clear.

-- *Beta-lactams*: Ampicillin for many years was the antimicrobial of choice for treatment of *H. influenzae*. Resistance is now common, mediated by either beta-lactamase production or chromosomal mutation. Ceftriaxone resistance has been identified, but remains relatively rare.

-- *Other antimicrobials*. Resistance to co-trimoxazole and chloramphenicol is relatively common. The consequences for clinical outcome in pneumonia have not been thoroughly evaluated. Co-trimoxazole is generally not used in cases of meningitis.

*Other microorganisms*

-- *Streptococcus pyogenes* (Group A *Streptococcus*): Resistance has not been detected against the drug of choice, penicillin. Resistance to macrolides is common, and is a public health concern in the treatment of bacterial pharyngitis.

-- *Moraxella (Branhamella) catarrhalis*: *M. (B.) catarrhalis* is a less frequent cause of respiratory infections. For decades the treatment of choice was penicillin, but in many parts of the world, most of these organisms are now resistant as a result of beta-lactamase production. Antimicrobials with activity include macrolides, tetracyclines, amoxicillin/clavulanic acid, cephalosporins, chloramphenicol, fluoroquinolones, and co-trimoxazole.

-- "Atypical" pathogens: "Atypical" pneumonia is most frequently caused by *Mycoplasma pneumoniae*. Other etiologies include *Chlamydia* spp., *Legionella pneumophila*, and a variety of respiratory viruses. For most cases, a macrolide (erythromycin, azithromycin, clarithromycin), tetracycline, or fluoroquinolone is effective. Resistance among these organisms has not been a major concern.

-- *Neisseria meningitidis*: Resistance to penicillin is rare. "Decreased susceptibility" has been recognized but is of uncertain clinical importance. Chloramphenicol resistance is rare. Rifampicin resistance has been recognized as a cause of prophylaxis failure.

-- *Listeria monocytogenes*: This organism is a relatively infrequent cause of meningitis. Penicillin and ampicillin are the drugs of choice. Resistance has been identified in isolated cases, but is rare.

## *Surveillance priorities*

There are a number of difficulties associated with surveillance of resistance in respiratory pathogens: relevant clinical samples can be difficult to obtain; several of the organisms are fastidious, and are thus difficult to collect, transport, and isolate reliably; identification of potential pathogens from sputum cultures with multiple colonies requires trained, alert, and motivated technologist; and reliable susceptibility testing of fastidious organisms often requires special media, incubation conditions, and test methodologies. Furthermore, laboratory findings of resistance in some instances has not been found to compromise treatment outcome in respiratory illnesses. On the other

hand, resistance in meningitis is clinically important, and STGs should ensure a high rate of effective therapy in the management of patients with meningitis.

1. Proportion of various pathogens. In developing treatment guidelines and in evaluating the potential utility of various vaccines, surveillance coordinators should ascertain the relative proportions of the most common viral and bacterial etiologic agents causing respiratory illnesses and meningitis. As there may be seasonal patterns in these proportions, data analysts may wish to stratify results by time period.

2. *Streptococcus pneumoniae*: The antimicrobials of greatest interest include beta-lactams (penicillin, third-generation cephalosporins), co-trimoxazole, and macrolides. Other antimicrobials to consider include fluoroquinolones, vancomycin, doxycycline, and chloramphenicol. For countries with an active vaccination program, serotyping may be usefully incorporated into the surveillance protocol.

   With disk diffusion testing of *S. pneumoniae* with oxacillin, it is possible to distinguish strains which are susceptible to beta-lactams from those which are likely non-susceptible. However, to distinguish between strains with intermediate- and high-level resistance, an MIC method is recommended.

3. *Haemophilus influenzae*: Susceptibility testing of *Haemophilus* is particularly problematic. By NCCLS recommendations [21, 26] susceptibility testing should be performed with HTM (*Haemophilus* Test Medium), but several laboratories have reported difficulty with this medium with a number of strains. Some laboratories continue to use chocolate agar for which there are no official interpretative standards currently available. Beta-lactamase production can be reliably detected by instant spot tests, for example with nitrocefin disks. More complete testing may include ampicillin, ceftriaxone, chloramphenicol, and co-trimoxazole. Co-trimoxazole should not be tested on chocolate agar as reports of false resistance are common. If feasible, determination of Type B strains may be useful, particularly if the country has an active vaccination program.

Table 2. Etiologies of respiratory diseases and meningitis, recommendations for therapy, and priorities in resistance [1] [9].

3GC = third-generation cephalosporin, FQ = fluoroquinolone, AMC = amoxicillin/clavulanic acid, AMP = ampicillin, CHL = chloramphenicol, ERY = erythromycin, PEN = penicillin, SUL = sulfisoxazole, RIF = rifampicin, TET = tetracycline, SXT = co-trimoxazole (trimethoprim/ sulfamethoxazole), VAN = vancomycin

| Organism | Antimicrobial Therapy? | Some antimicrobial options | Important Resistance? |
|---|---|---|---|
| **Acute otitis media** | | | |
| ***Bacterial*** | | | |
| *Streptococcus pneumoniae* | Yes | AMP, SXT, ERY/SUL, Oral Ceph. | Yes |
| *Haemophilus influenzae* | Yes | AMP, AMC, SXT, ERY/SUL, Oral Ceph. | Yes |
| ***Other*** | No | None | No |
| Respiratory viruses | | | |
| **Community-acquired pneumoniae** | | | |
| ***Bacterial*** | Yes | PEN, AMP, SXT, CHL, ERY, FQ | Yes |
| *Streptococcus pneumoniae* | Yes | PEN, AMP, AMC, SXT, CHL, FQ | Yes |
| *Haemophilus influenzae* | Yes | AMC, TET, SXT, CHL, ERY, FQ | Yes |
| *Moraxella (B.) catarrhalis* | Yes | ERY, TET | No |
| *Mycoplasma pneumoniae* | Yes | ERY, TET | No |
| *Legionella pneumophila* | No | None | No |
| ***Other*** | | | |
| Respiratory viruses | No | None | No |
| **Other respiratory infections** | | | |
| ***Common cold*** | No | None | No |
| Respiratory viruses | Yes | PEN, ERY | No |
| ***Pharyngitis*** | | | |
| Respiratory viruses | Yes | PEN, 3GC, VAN, CHL, RIF | Yes |
| *Streptococcus pyogenes* | Yes | 3GC, CHL | Yes |
| **Meningitis** | Yes | PEN, 3GC, CHL | No |
| ***Bacterial*** | | | |
| *Streptococcus pneumoniae* | No | None | No |
| *Haemophilus influenzae* | | | |
| *Neisseria meningitidis* | | | |
| ***Other*** | | | |
| Enteroviruses, other viruses | | | |

## 10.3 Urethritis and cervicitis

### *Etiology*

The successful treatment of all identified cases of urethritis and cervicitis, including gonorrhea, is an important public health priority [108]. Besides the significant discomfort experienced by symptomatic individuals, untreated infection can lead to pelvic inflammatory disease, ectopic pregnancies, and infertility in women and to increased rates of transmission of the HIV virus and other agents of sexual transmitted infections (STIs). The two most common causes of urethral and cervical discharge are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, frequently identified together in co-infections. Infection in men is usually symptomatic, while infection in women can be asymptomatic and is thus often unrecognized.

### *Therapy*

Therapy should always cover both of the main pathogens, even if only one is confirmed on laboratory testing. This could be accomplished by the use of a single agent active against both pathogens, such as azithromycin, or through the use of two agents, for example ceftriaxone and doxycycline [108, 109].

*Neisseria gonorrhoeae*: For decades, penicillin remained the drug of choice for treating urethral discharge. Unfortunately, resistance to penicillin is now common, necessitating the use of alternative agents. Other compounds with activity against *N. gonorrhoeae* include ciprofloxacin, azithromycin, ceftriaxone, cefixime, spectinomycin, kanamycin, and co-trimoxazole [110, 111].

*Chlamydia trachomatis*: Drugs effective in the treatment of chlamydial disease include doxycycline, erythromycin, azithromycin, amoxicillin, erythromycin, ofloxacin, and tetracycline.

### *Resistance issues*

Resistance is an important issue to consider in the development of national guidelines for the treatment of bacterial sexually transmitted infections [41, 112-114]. As laboratory tests of antimicrobial susceptibility resistance correlate well with observed clinical outcome, surveillance of clinical isolates from urethral and cervical discharges is an important component in many countries in the evaluation and adaptation of treatment guidelines. WHO recommends that first-line antimicrobials be active in at least 95% of patients [43].

*Neisseria gonorrhoeae*: In addition to the penicillin resistance mentioned above, resistance to many other agents is common and rising. Of

particular concern is resistance to ceftriaxone, cefixime, spectinomycin, and fluoroquinolones [115].

*Chlamydia trachomatis*: Resistance is not common in *Chlamydia* and is not a concern in the development of STGs.

Table 3. Etiologies of urethritis and cervicitis, recommendations for therapy, and priorities in resistance [1, 43].

3GC = third-generation cephalosporin, FQ = fluoroquinolone, AZI = azithromycin, DOX = doxycycline, ERY = erythromycin, SPE = specinomycin

| Organism | Antimicrobial Therapy? | Some antimicrobial options | Important Resistance? |
|---|---|---|---|
| **Urethritis and cervicitis** | | | |
| ***Bacterial*** | | | |
| *Neisseria gonorrhoeae* | Yes | 3GC, SPE, AZI, FQ | Yes |
| Chlamydia trachomatis | Yes | DOX, ERY, AZI, FQ | No |

## *Surveillance priorities*

Adequate surveillance of organisms causing urethritis and cervicitis is compromised by a few factors: limited number of cultures taken from patients who are usually treated empirically, difficulty in obtaining proper specimens (urethral swabs in men, cervical swabs in women), and difficulty in transporting, isolating, and susceptibility testing fastidious organisms. To obtain the most valuable statistics, a protocol for systematic sampling of patients with urethral and vaginal discharges may be advised.

1. *Neisseria gonorrhoeae*: When penicillin resistance was the drug of choice, monitoring of the rate of beta-lactamase production in clinical isolates was sufficient for following resistance trends and suggesting the need for a switch in first-line therapy. Since penicillin resistance is now common, susceptibility testing of a full panel on GC medium of relevant agents is recommended. Priority antimicrobials include penicillin, ceftriaxone, spectinomycin, and fluoroquinolones.

# 11. Development of Standard Treatment Guidelines in populations with HIV/AIDS

Most of the recommendations provided above are oriented towards patients who are not infected by HIV. For such patients, syndromic management with empiric therapy can provide reasonable clinical outcomes for the majority of individuals. However, in populations with high rates of infection, cure rates may be significantly compromised as a result of several factors: incorrect

diagnoses and infection with atypical pathogens; lowered immune status as a result of HIV infection, malnutrition, and concomitant infections; and higher rates of resistance due to higher rates of exposure to antibiotics as a result of prophylactic or previous therapeutic interventions. Adequate management of such patients -- proper diagnosis, therapy, monitoring -- often depends on access to laboratory facilities with sufficient expertise and experience.

More detailed guidelines for the management of such patients can be found in a number of internationally available publications and guidelines, including the *WHO Model Prescribing Information: Drugs used in sexually transmitted diseases and HIV infection* [7]

## Decision Guide to Develop, Adapt or Modify an Infectious Disease Standard Treatment Guideline

## Introduction

In reviewing a policy and/or a treatment guideline in order to make rational choices, a process of consensus building and decision-making should take place that involves all key stakeholders. Other factors that would need to be taken into consideration: methodological, geographical and temporal variation of resistance prevalence rates, treatment failures definitions, clinical failures measured by acceptable clinical rate, availability and accessibility of replacement therapy, cost, etc. In developing countries, approaches can be on a micro or macro intervention level depending on available resources and degree of antimicrobial resistance on selected, key pathogens.

The establishment of a guideline requires a rigorous process that should be guided by the Drug and Therapeutic Committee (DTC). General recommendations to establish clinical guidelines can be found in the Standard Treatment Guidelines document used by the Rational Pharmaceutical Management Plus Program of Management Sciences for Health (MSH) [116].

## Objective:

To provide an easy-to-use tool to guide the national Standard Treatment Guidelines (STG) committee and hospital Drugs and Therapeutics committees (DTC) in the appropriate use of antimicrobial resistance (AMR) surveillance data for the adaptation of STGs.

## Audience:

Drug and Therapeutic Committee (DTC) and Standard Treatment Guideline (STG) members, whose task is to adapt, modify and develop Standard Treatment Guidelines for infectious diseases every two years.

## Methodology

In developing an infectious disease standard treatment guideline the following easy-to-use decision steps are recommended (not necessarily in this order):

## Data Sources:

1. Prioritize the most common infectious diseases in the country based on morbidity, mortality and costs. Obtain a list of infectious diseases responsible for most consultations (morbidity) and deaths (mortality) at all level of care.

2. Obtain mortality rates for previous 3 years and trends for those infectious diseases to have it as baseline indicator. Mortality rates if available can be used to compare before and after an intervention is implemented.

3. Obtain antimicrobial resistance rates and trends for pathogens chosen
   Antimicrobial resistance rates reflect antimicrobial usage and serves as a warning to monitor and possibly restrict a particular antimicrobial agent. Antimicrobial resistance trends on the other hand reflect the use of an antimicrobial agent over time.

4. Document and analyze antimicrobial drug prescribing behavior by level of care. Conduct small study to learn prior prescribing practices before implementing STGs. Prescribers' knowledge, attitudes and behavior (KAB) should provide information and corrective measures could be instituted. Prescribing indicators can assist to evaluate before and after intervention [117, 118].

5. Gather local practitioner/clinician-derived consensus practice
   Experience accumulated by prescribers over time provides an important input for DTCs when selecting a first, second and third-line antimicrobial agent for a particular infectious disease.

6. Use of regional AMR surveillance data (e.g, ANSORP [47]
   Knowledge of existing AMR surveillance data in the region is an important alternative when lacking local data. In addition, provides access to and cooperation with a network of interested individuals and experts in the field.

7. Use of online antibiotic management databases (e.g, John Hopkins Division of Infectious Diseases Antibiotic Guide [119]
   Free of cost antibiotic guide management databases are now available online. There are also online, free-of-cost, e-prescribing PDA software that provides pricing, dosing, drug interactions, contraindications and off-label indications and can be used as reference. These systems can assist DTCs to obtain accurate information on an antimicrobial (side effects, dosage, warnings, etc).

8. List and describe antimicrobials available at different level of care (sub-health posts, health posts and national).
   Availability of antimicrobials listed on approved formulary by the MOH must be secured at all level of care.

## Data Uses:

9. Define and establish criteria for AMR alert thresholds for key pathogen Resistance Alert Threshold (RAT): The maximum allowable prevalence of resistant bacteria isolated from a group of patients that does not pose an unacceptable risk to general human health population receiving the antimicrobial of choice.

10. Prepare a table that includes key infectious diseases and pathogens, local resistance rates to first-line antimicrobials, resistance thresholds, disease-specific therapy thresholds, Nepal Standard Treatment Schedules for Sub-health posts and health posts, Alternative Antimicrobial Agent (if available) and reference therapy options from the WHO Prescribing Guide for Bacterial Infections (see table example below)

11. Collection of international, regional and/or local published guidelines (WHO prescribing guide for bacterial infections) [43]
    Published guidelines can serve as a reference when DTC selects an antimicrobial agent. However, DTC must keep in mind list of antimicrobial listed and approved in country formulary. If evidence shows that an unavailable antimicrobial must be included, DTC should recommend their respective MOH to purchase it and include in formulary. Example, if a new TB regimen (DOTS, DOTS-Plus) is planned to be instituted, then needed drugs must be included and secured for population in-demand.

12. Assess possible biases in data.
    DTC should raise questions to assess whether the surveillance data is representative and accurate (see section 1.4.6.). Examine data carefully and assess disparities observed during internal and external quality control of isolates identification and antimicrobial susceptibility testing

## Outcomes and Indicators

13. Select antimicrobial drug use indicators [118]
    Antimicrobial drug use indicators are an objective way to measure drug use patterns and prescribing behavior. The Rational Pharmaceutical Management Plus Program at Management Sciences for Health has put together a working draft on antimicrobial drug use in hospitals [118, 120].

14. Select antimicrobial resistance indicators by priority area
    Indicators for monitoring progress are needed in order to assist decision-makers and policy-makers at all levels of care and to increase focus on sustainable management of antimicrobial resistance. They can provide

an early warning, sounding the alarm in time to prevent economic, social and environmental damage. APUA suggests indicators by priority areas for chapters (grassroots country-based groups) to evaluate and to measure progress in priority areas outlined in each stated strategic objective. These indicators can be discretely modified and adapted to local circumstances.

15. Establish expected clinical outcomes
    - treatment failures
    - rate of adverse effects,
    - quality of life attributes
    - patterns of AMR,
    - survival rates
    - mortality,
    - length of hospital stay,

16. Determine expenditures of antimicrobial drugs and then calculate percentage allocated by level of care.
    DTCs can obtain pertinent information on drug costs incurred by government and then calculate percentage of drugs allocated and used by practitioners by level of care. This information serves to monitor expenditures by level of care and indirectly provide information on antimicrobial usage.

    It is strongly recommended that the established guideline should be revised at least annually and not later than three years. A new study suggests that most practice guidelines are outdated after five years [121].

## Table 1. Generic worksheet for applying country resistance rates to therapy recommendations

| Key Infections | Antimicrobial Resistance Parameters | | | Treatment Options | | |
|---|---|---|---|---|---|---|
| | Resistance Rates in Country | Antimicrobial Resistance Threshold | Antimicrobial Therapy Threshold | Country STG Recommendations | WHO Prescribing Guides | Other Alternatives |
| Gonorrhea | *N. gonorrhoeae* | *N. gonorrhoeae*<br>First-line: 3-5%<br>(WHO, GASP) | All suspected or confirmed cases | | Ceftriaxone<br>Spectinomycin<br>Ciprofloxacin | Azithromycin<br>Fluoroquinolones |
| Meningitis | *S. pneumoniae*<br><br>*H. influenzae*<br><br>*N. meningitidis* | *S. pneumoniae*<br>PEN: 10% R (2)<br>(WHO Prescribing Guidelines)<br><br>*H. influenzae*<br>No recommendations<br><br>*N. meningitidis*<br>Little resistance | All suspected or confirmed cases<br><br>All suspected or confirmed cases<br><br>All suspected or confirmed cases | | For penicillin-susceptible:<br>Penicillin, ceftriaxone<br>For penicillin-intermediate:<br>Ceftriaxone<br>For penicillin-resistant:<br>Ceftriaxone + vancomycin + rifampicin<br><br>Ceftriaxone<br>Ampicillin, chloramphenicol if %Resistant is low<br><br>Penicillin + chloramphenicol | Chloramphenicol |
| Pneumonia | *S. pneumoniae*<br><br>*H. influenzae*<br><br>*M. pneumoniae* | *S. pneumoniae*<br>PEN: 20% R (7)<br>(Rotschafer presentation)<br>Macrolide: 10% R (8)<br>(ESAC Working Group)<br><br>*H. influenzae*<br>No recommendations<br><br>*M. pneumoniae*<br>Little resistance | Moderate or severe respiratory distress<br><br>Moderate or severe respiratory distress<br><br>Moderate or severe respiratory distress | | Specific recommendations depend on age group and suspected etiology<br><br>Amoxicillin, erythromycin, doxycycline, SMX-TMP, penicillin, chloramphenicol, cefuroxime, ceftriaxone, penicillin + gentamicin, cefotaxime<br><br>For *Mycoplasma*:<br>erythromycin | Amocillin/Clav.<br>Tetracycline<br>Fluoroquinolones |

| Key Infections | Antimicrobial Resistance Parameters | | | Treatment Options | | |
|---|---|---|---|---|---|---|
| | Resistance Rates in Country | Antimicrobial Resistance Threshold | Antimicrobial Therapy Threshold | Country STG Recommendations | WHO Prescribing Guides | Other Alternatives |
| Watery diarrhea<br>Childhood, food-borne, traveller's | Pathogenic *E. coli*, *Salmonella*<br>No data | Pathogenic *E. coli*, *Salmonella*<br>No recommendations | Severe dehydration<br>Suspected cholera | | Usually none indicated<br>SMX-TMP, ciprofloxacin | Doxycycline<br>Ampicillin<br>Ceftriaxone |
| Cholera | *V. cholerae*<br>R | *V. cholerae*<br>No recommendations | All confirmed or suspected cases | | Doxycycline, ciprofloxacin | Tetracycline<br>Erythromycin<br>Ampicillin<br>SMX-TMP |
| Parasitic | *Giardia lamblia* | *Giardia lamblia*<br>No resistance | All confirmed or suspected cases | | Metronidazole, tinidazole | |
| Dysentery<br>Bacterial | *Shigella* species | *Shigella* species<br>No recommendations | Severe dehydration<br>Suspected dysentery | | Nalidixic acid, ciprofloxacin | Amoxicillin<br>Ampicillin<br>SMX-TMP<br>Chlorampenicol<br>Tetracycline |
| Parasitic | *Entamboeba* sp.<br>No data | *Entamboeba* sp.<br>No resistance | All confirmed or suspected cases | | Metronidazole + diloxacine furoate | |
| Malaria | *P. falciparum*<br>No data | *P. falclparum*<br>7-day test: 25%<br>RI+RII: 25%<br>RIII: 14%<br>ETF+LTF: 25%<br><br>For definitions, see reference Shretta | All suspected or confirmed cases | | Blood stage:<br>Chloroquine, sulfadoxine + pyrimethamine, mefloquine, quinine + tetracycline, artesiminin, artesunate, halofantrine<br><br>Tissue stage:<br>Primaquine | Atovaquone |
| Tuberculosis | *M. tuberculosis*<br>No data | *M. tuberculosis*<br>INH: 4% R<br>(CDC, American Thoracic Society)<br><br>MDR-TB: 9.6%<br>(Brewer, United States, American Thoracic Society) | All suspected or confirmed cases of active disease<br><br>Treatment of carriers depends on local guidelines and resources | | Four treatment categories are defined. Combinations may include:<br>INH, RIF, PYR, EMB, STR, THI<br>Additional agents for MDR-TB:<br>Kanamycin, amikacin, capreomycin, ethionamide, prothionamide, ofloxacin, ciprofloxacin, cycloserine, para-aminosalicyclic acid | |

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