SURVEILLANCE OF ANTIMICROBIAL RESISTANCE: WESTERN PACIFIC REGION
TEN YEARS EXPERIENCE AND FUTURE DIRECTIONS

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The development over the past 65 years of drugs that kill infecting microbes without harming the patients infected has cured more illness and preserved more productive life than any other advance in the history of medicine.

As treatment with each such antimicrobial agent became widespread, however, it usually began to fail as microbes became resistant to it. Replacing failing older agents was difficult in much of the world because newer agents were expensive. It is now difficult everywhere because new agents are not becoming available.

Recognition of this growing health problem, of its cause by overuse of antimicrobials and its of epidemic spread led in 1998 to a World Health Assembly Resolution urging Member States to take steps to contain antimicrobial resistance and in 2001 to a WHO Global Strategy program that elaborates those steps.

After holding a series of meetings with specialists from nations in the Region, the Western Pacific Regional Office of WHO had begun to implement parts of that strategy more than a decade ago by drawing up model guidelines for antimicrobial use and by initiating a program for surveillance of antimicrobial resistance. Each of the 13 nations ultimately participating reported annually from 1991 – 1998 (except for 1993) the percentages testing resistant at one or more laboratories in that nation to each of designated sets of antimicrobial agents of isolates of 22 species of bacteria. Tabulations of those percentages were shared with the participants and are now reviewed here in this report.

The percentages of isolates of many species reported resistant to many of the agents in many of those nations are among the highest reported anywhere. Yet low percentages are reported in other nations of the Region. Accordingly, tenfold or greater nation-to-nation differences in prevalence of
resistance to some agents are seen here for some species. The compiled data does not allow study of sampling or testing variations, but they seem unlikely to explain such differences. In both countries with low and with high percentages resistant, moreover, discernable trends over time are usually towards increasing resistance.

- Less varied between nations or over time was resistance among *Escherichia coli* to oral agents long used in the community, such as tetracycline, ampicillin or trimethoprim-sulfamethoxazole, which was seen in about 1/4 to 3/4 of the isolates. An unprecedented 1/5 to 1/2 of the *E. coli* isolated in many of the Region’s nations had became resistant to fluoroquinolone after only a decade of its use, however, while less than 5% had in 3 other nations. While resistance to an agent may thus reach some equilibrium eventually, it appears to be reaching it much sooner in many nations of this Region.

- Resistance also increased in other community-acquired pathogens. Resistance to penicillin rose over the decade to around 1/5 of the isolates of *Streptococcus pneumoniae* in most of the nations, but to more than 3/4 in one country, the most ever reported. Most isolates of *Shigella flexneri* were resistant to all available oral agents except for fluoroquinolones. Multi-resistant *Salmonella typhi* were reported from three nations, where they accounted for 1/4 to 1/2 of the isolates.

- Resistance to many agents also increased among hospital-acquired pathogens. The fraction of all isolates of *Staphylococcus aureus* from the Region that were methicillin-resistant rose over the decade from less than 1/4 to more than 1/3, and rose faster in countries where it had initially been low. In many countries so many isolates of *Acinetobacter* and *Enterobacter* were resistant to each tested agent as to suggest that many are resistant to all of them. Extended-spectrum â-lactamases (ESBLs) remain rare in isolates of *Klebsiella pneumoniae* of several nations but are in up to 1/3 of those in the others. In isolates of *Pseudomonas aeruginosa* from the Region resistance to ceftazidime rose from 13% to 17% and to fluoroquinolones from 16% to 23%.
• The percentages of isolates reported resistant from many of the Region’s most populous nations are thus among the highest, and many the highest, yet reported anywhere and are increasing in countries where they are still low. This will mean frequent treatment failure, costly efforts to try newer agents and near-prohibitive risks for hospital-based procedures.

• The known remedial responses to this growing menace are set forth in the comprehensive *WHO Global Strategy for Containment of Antimicrobial Resistance*. Their implementation will be difficult for any nation, however, and for different reasons in different nations. It would be helped enormously by Regional Office support of training and of ongoing, active collegial experience- and resource-sharing among those undertaking implementation in the Region’s nations.

• The WPRO Antimicrobial Resistance Surveillance Program, reviewed here, has been a valuable initiative within this framework. It has outlined problems in the Region and made contact with some of those working to contain them. Improved information technology in these nations can now support a more advanced system that will expand the data, assure its quality, explore its epidemiological basis and allow multi-level analyses to both manage resistance locally and trace its spread in the Region. A special benefit of the interactive networks that would develop with such a system is that they can identify, connect and involve in a model of continuous quality improvement workers who are in a position to implement other parts of the *WHO Global Strategy*. 
The nature of antimicrobial resistance

When antimicrobial agents were first used sixty years ago, they could cure nearly all bacterial infections, which were then the major cause of death. They could diffuse through a patient’s tissues and kill the relatively small numbers of what was usually a single strain of bacteria infecting some secluded site in those tissues.

The great flaw of those agents, as we know now, was that they were also quietly killing much larger numbers of very many strains of bacteria that were not infecting but only colonizing the patient’s mouth, skin and guts. Those bacteria were not secluded, but open to the environment and to other people.

After an antimicrobial agent had devastated vast populations of bacteria in this way, a strain of bacteria resistant to the agent eventually emerged somewhere. That strain made a protein that blocked or circumvented the agent’s lethal effect on the strain \[1, 2, 3\].

Each such protein was expressed by a resistance gene. The gene might be encoded on the chromosome of the strain, and so spread only in that strain. Alternatively, it might be on a plasmid, a mobile genetic element often able to transfer itself to other strains or species.

Mobile subunits within the plasmid, such as integrons or transposons, might move the gene to a second plasmid able to transfer to strains inaccessible to the first. The resistance gene could then get into strains and species of bacteria that might vary in their access to niches in microbial ecosystems and in their ability to infect.
All such processes for spread of a resistance gene were driven by exposure to the agent. A single resistant bacterium is kept rare by its competing susceptible neighbors until the agent kills them and allows it to overgrow many-fold overnight to replace them.

That multiplication increases the chance of the resistance gene being inserted into another genome, where it might be near a gene encoding resistance to a different agent. Such linkage enables either agent thereafter to co-select for and drive the spread of both genes.

Driven in this way over the past sixty years by successive generations of antimicrobial agents hundreds of resistance genes have emerged, multiplied, converged in linkages to one another, entered into multiple genetic elements and bacterial strains and species, and so spread widely through the world’s interconnecting bacterial populations.

The results are that many of the antimicrobial agents that once killed nearly all kinds of infecting bacteria are now ineffective against large percentages of many kinds and nearly all of others, and that newer agents are losing effectiveness in the same way. As the problem grows, more patients fail therapy and remain infected or die [1, 2, 3]

**Management and control of resistance**

The nature of antimicrobial resistance makes it hard to control. Bacterial populations are enormous and diverse. The bacteria carried by each of us belong to hundreds of species and outnumber our own cells and the number of people in the world. Most are harmless, but some can infect anyone and many can infect those with impaired host defenses.

The bacterial populations which each of us hosts interconnect with those of other human and animal hosts throughout the world. They thus form pathways for spread of resistant strains of bacteria, resistance genes and the genetic vectors that carry those genes.

Such host-to-host spread of resistance is driven by antimicrobial usage. A strain resistant to an agent may remain rare on an untreated host and thus be unlikely to be among any strains passed on. Exposure to the agent amplifies the resistant strain, however, making it more likely to be passed on to a second host, who, if treated, may then give it to a third.
A resistance gene in a strain of bacteria infecting a patient, therefore, is very unlikely to have emerged in that strain while it was in or on that patient. It probably emerged years earlier in another strain in another host perhaps on another continent, and then moved from one treated host to another until it eventually reached the strain infecting the patient.

There are thus basically only two ways to control resistance: reduce the number of antimicrobial-treated hosts, or reduce the spread of bacteria between hosts [1, 2, 3].

Perfect application of either would be effective. Without treatment, a resistant strain might not multiply enough in a host to be passed on to another host. Alternatively, if hosts were hermetically sealed off from one another, the bacteria of any host could acquire resistance only by a quite rare event, the new emergence of a resistance gene.

The obstacles to perfect application are, of course, that some hosts need treatment and that complete isolation of any host is difficult in the real world. Therefore, management of resistance must integrate optimal selection of antimicrobials for just those hosts who need them with optimal containment of host-to-host spread of resistant bacteria.

**The need for information in the management of resistance**

Optimal use of antimicrobial agents and containment of resistant bacteria both need information. Information is needed locally to monitor the bacteria infecting or colonizing patients in each medical center and community, nationally to see trends and guide policy and globally to detect and trace epidemics. Its general purpose is surveillance.

Surveillance of antimicrobial resistance has been discussed by many groups of experts convened over the last twenty years to address the problem of antimicrobial resistance. A summary of those discussions by sixteen of the groups is available [4].

The expert groups have recognized that antimicrobial resistance impacts many different types of health care workers, including clinicians, microbiologists, epidemiologists and researchers, and that each needs different kinds of information from surveillance. Many elements of surveillance thus need to be integrated [2, 3, 4].
Data for surveillance of resistance originates in microbiology laboratories. Bacteria are invisible except in such laboratories, which isolate and identify the bacteria and test their resistance to antimicrobials. Nearly all of the data that exists is in the reports of clinical laboratories on the bacteria they isolate from individual patients to guide their treatment.

The report on each such isolate usually includes its species and the measurements of its susceptibility to each of a set of antimicrobial agents, as well as the patient’s identity, age, sex, location and body site cultured. The report goes to the patient’s record and a copy to a file, both either on paper or increasingly in computerized reporting systems.

The surveillance information is in the interrelationships between the terms and values in the accumulated reports. For example, how many patients at what locations in a hospital or community had isolates from blood of a certain species resistant to certain agents last month compared to preceding months or to other parts of the hospital or community, etc?

The reports thus need to be analyzed to produce surveillance information. Unfortunately, few of the world’s microbiology laboratories can analyze their reports. Analyzing paper files is too much work, and the computerized reporting systems now in use are designed only to transmit reports and so provide few or no analytical options.

A laboratory can analyze its reports if it enters them into a database or downloads them into one from a computerized reporting system. The database may then be queried repeatedly for the information needed to manage ongoing local resistance problems.

**Surveillance for the local management of resistance**

The most immediate uses of such database queries are local, at the medical center and community served by the laboratory. The microbiologist can screen the data in various ways to monitor patterns of culture usage or quality of test performance or can read presumptive mechanisms of resistance into shifting resistance phenotypes.

Clinicians can query the database to adjust empirical antimicrobial therapy to the levels of resistance observed for different times and different patient locations, e.g. infections in one intensive care unit that year or infections in children in the community in recent years.
Pharmacists may need similar analyses to update the antimicrobial formulary.

Infection control can ask the database whether methicillin-resistant *Staphylococcus aureus* (MRSA) were less frequently isolated on certain wards last month after a special intervention, or whether more MRSA are becoming rifampicin-resistant on certain wards or vancomycin-resistant enterococci (VRE) more linezolid-resistant on others.

Besides using the database to monitor such known nosocomial problems, infection control can also ask it to flag new isolates with distinctive resistance phenotypes and to provide dates and locations of prior matching isolates. This makes it possible to detect, trace and contain new resistance problems before they become large outbreaks.

**Multi-center or national surveillance networks**

Medical centers using such databases to manage their local resistance problems can easily merge their databases to form a multi-center surveillance database. Patient identification in each database can be “hashed” before merging for patient confidentiality. The merged database then retains all the other information in the databases of the contributing centers.

The detailed information retained in a merged multi-center database makes it possible to evaluate center-to-center variance in resistance and testing and center-to-center spread of resistant strains. Ongoing collegial evaluations of these kinds by participating centers can be the basis for continuous quality improvement of the management of resistance.

The advent of databases on personal computers thus provides orders of magnitude more information for understanding and managing resistance. Earlier paper-based surveillance tallied overall percent resistant to each agent for each species at each center and averaged them for national surveillance. Further analyses were not available locally or nationally.
The surveillance data reviewed in this report

This report reviews data submitted to the WHO Western Pacific Region (WPRO) Antimicrobial Resistance Surveillance Programme for each year, except 1993, from 1991 through 1998. Each nation in the Programme had filled out and sent to WPRO each year a paper form listing the numbers tested and percentages resistant to sets of antimicrobial agents of isolates of twenty-two clinically significant species of bacteria (see Tables 1 and 2).

<table>
<thead>
<tr>
<th>Table 1. Countries included in this report.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
</tr>
<tr>
<td>China — Beijing, Shanghai</td>
</tr>
<tr>
<td>Fiji</td>
</tr>
<tr>
<td>Hong Kong, China</td>
</tr>
<tr>
<td>Japan</td>
</tr>
<tr>
<td>Republic of Korea</td>
</tr>
</tbody>
</table>

Many of those centers have local databases, which they could analyze for values to put on the paper forms. WPRO later entered those values into an Excel database to list percent resistant by species, nation and year. Interposing the paper summary, however, blocked transfer of much of the detailed information in the local databases to the WPRO database.

The detailed information in the local databases would allow many kinds of analysis that could clarify and enrich the summarized data. Even without this detail, however, the existing WPRO database provides an extremely valuable overview of the very wide range, trends and divergence of the resistance problems in the nations of this Region.
Table 2. Microorganisms covered in this report.

<table>
<thead>
<tr>
<th>Category</th>
<th>Microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial and community pathogens</td>
<td><em>Escherichia coli</em> (urine, non-urine)</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Respiratory pathogens</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td><em>Moraxella (Branhamella) catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Enteric pathogens and enteric fever</td>
<td><em>Salmonella non-typhi, non-paratyphi A</em></td>
</tr>
<tr>
<td></td>
<td><em>Salmonella paratyphi A</em></td>
</tr>
<tr>
<td></td>
<td><em>Salmonella typhi</em></td>
</tr>
<tr>
<td></td>
<td><em>Shigella</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td>Other community pathogens</td>
<td><em>Citrobacter freundii</em></td>
</tr>
<tr>
<td></td>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td></td>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td></td>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td></td>
<td><em>Providencia</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus saprophyticus</em></td>
</tr>
<tr>
<td>Nosocomial pathogens</td>
<td><em>Acinetobacter</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Serratia</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus, coag.-negative (Blood)</em></td>
</tr>
</tbody>
</table>

A geographic breakdown of data submitted is depicted in Figure 1, highlighting a great disparity in number of isolates submitted by countries in the region reflecting differences in the frequency of diagnostic testing in routine clinical care and in the number of centers participating in the surveillance collaboration. In some countries, results reflect the experience of only one or a few medical centers, while in others, larger numbers of centers permit a broader geographic and demographic representation of the national experience.
The frequency of organisms represented in the database is presented in Figures 2 and 3. Though these figures are heavily influenced by the Australian and New Zealand experiences, most countries when viewed individually exhibited broadly similar trends. The most common organisms were *E. coli*, *S. aureus*, *K. pneumoniae*, and *P. aeruginosa* followed by a number of other common community and hospital pathogens. With some notable exceptions, epidemic-associated pathogens, such as *S. dysentariae* and *S. typhi* were infrequent. The low number of fastidious organisms, such as *S. pneumoniae* and *H. influenzae*, seen in some countries may be attributable to problems in laboratory capacity or to features of the patient populations represented.
Figure 2. Number of isolates by organism in 1998 for the most frequent bacterial species (1996 or 1997 for some countries and organisms).

Figure 3. Number of isolates by organism in 1998 for the less frequent bacterial species (1996 or 1997 for some countries and organisms).
RESULTS

Acinetobacter species

Acinetobacter, predominantly baumannii, are often isolated from respiratory specimens of patients in hospitals, and especially those in intensive care units and on ventilators. It is usually difficult to know whether they are truly infecting or only colonizing the respiratory tract. Because these patients may be severely ill, however, it is also difficult to withhold antimicrobial therapy.

A few nosocomial strains of Acinetobacter circulating in a hospital may thus be repeatedly targeted for treatment with antimicrobials, often unnecessarily. In the process those strains may become resistant to many of those agents, and sometimes even to newer agents not tested here, such as cephemycins.

Overall, between a quarter and a half of the isolates of Acinetobacter surveyed here were resistant to any of the antimicrobials tested. The lower rates of resistance to amikacin would often not be helpful because it and other aminoglycoside antibiotics may attain only marginally effective concentrations in respiratory tissues.

The only analyses possible with these data, overall percentage resistant to each antimicrobial agent, do not reveal linkage of resistance to different agents. Other studies, however, have shown such linkage to be prevalent in isolates of Acinetobacter. Many of these isolates were thus probably resistant to nearly all of the tested agents, and some to all of them. Such isolates from severely ill patients, whether invasive or not, will provoke use of expensive new agents and so make it likely that such strains of Acinetobacter will be among the first to become resistant to those new agents also.

Taken altogether, the isolates of Acinetobacter from all of the countries show few trends over the nineties, except for increasing resistance to ceftazidime and perhaps also to fluoroquinolones. The overall increase in resistance to ceftazidime could be accounted for largely by more substantial increases seen Australia, New Zealand, Malaysia, Philippines, and Korea (see Figure 4). Increases in
fluoroquinolone resistance were apparent mostly in Malaysia, Korea and China.

These changes are consistent with general observations made earlier. Although exceptions exist, resistance to many of the older antimicrobials seems to have reached equilibrium after several decades of use. Resistance to agents introduced more recently may rise more steeply. The steeper rise among isolates of *Acinetobacter* for resistance to ceftazidime or to fluoroquinolones may have already occurred before the nineties in some countries, appears to have been observed here during the nineties in several, and may not yet have occurred in still other countries, for example Japan in the data here.

**Figure 4. Antimicrobial resistance rates for cefotaxime in *Acinetobacter* species, 1991-1998.**

These apparent country-to-country differences may, of course, only be hospital-to-hospital differences. The data tables do not specify whether the data ascribed to a country is from one or multiple medical centers. Even if data were from multiple centers, however, its submission here as paper lists of data aggregated from those centers precludes analysis of center-to-center differences. Submission instead of electronic files in database format from each center would allow such analyses. Those files would also allow analyses of location-to-location, time-to-time and strain-to-strain differences within each center. Such distinctions could be essential for the delineation, understanding and management of resistance, especially in species like *Acinetobacter* that are predominantly nosocomial.
**Citrobacter freundii**

Strains of *C. freundii* appear from this data to be isolated from clinical specimens only a tenth to a third as frequently as strains of *Acinetobacter*. Overall, 4/5 of them tested resistant to ampicillin and nearly 3/4 to cephalothin, presumably because of chromosomally encoded ampC β-lactamases, while only a quarter to a third tested resistant to cefotaxime. For these β-lactam agents, there was little country-to-country variation.

Resistance to some other agents, which may have been acquired rather than an inherent characteristic of the species, showed considerable country-to-country variation. Resistance to fluoroquinolones, for example, which never exceeded 1% in New Zealand or 6% in Australia, was seen in a third to a half of the isolates from the Philippines or Singapore and in about a quarter of those from China or Korea. Roughly similar ranges for the same countries were seen for resistance to gentamicin.

**Enterobacter species**

*Enterobacter species*, usually consisting mostly of *Enterobacter cloacae* and *Enterobacter aerogenes*, appear to have been isolated slightly less often than *Acinetobacter* in some countries, but more often in others. This variation may represent differences in the extent to which *Acinetobacter* are a nosocomial problem.

*Enterobacter* also have an inducible ampC chromosomal β-lactamase, which makes them almost universally resistant to ampicillin and to first generation cephalosporins, such as cephalothin. This is reflected here in percentages testing resistant being around 90% or higher, with most of the remainder probably testing close to resistant, or intermediate.

The ampC becomes stably de-repressed, that is continuously expressed, in something like a quarter of *Enterobacter* isolates. Those isolates then test resistant to third generation cephalosporins, represented here by cefotaxime. This can be seen here in the isolates from Philippines, Malaysia, New Zealand and Japan which average about 20% resistant to cefotaxime. Percentages range up to about twice as high in Australia, China, Hong Kong and Singapore. It would be interesting to explore the reasons for these higher percentages, examining first perhaps extent of use of third generation cephalosporins in the patient care units that are contributing most of these isolates.
For the types of resistance that are not a species characteristic for Enterobacter, as is the ampC discussed above, there is more country-to-country variation. An exception to this is resistance to chloramphenicol. Resistance to chloramphenicol is acquired and is usually carried on a plasmid. In spite of the opportunity that this provides for variation in prevalence of resistance to chloramphenicol, and the wide variation that is often actually observed, the prevalence of resistance to chloramphenicol in isolates of Enterobacter in most of the countries surveyed here hovers around a quite consistent 20%, with twice-as-high rates seen only in China 2, Philippines and Vietnam.

Other types of acquired resistance exhibited country-to-country variation in prevalence among isolates of Enterobacter that approached tenfold. Resistance to gentamicin remained mostly below 3% in New Zealand, 6% in Japan and 10% in Australia and Fiji, but ranged up to 50% in Philippines and Vietnam. Percentages resistant to co-trimoxazole covered a similar range. Resistance to fluoroquinolones stayed mostly below 5% in Australia, New Zealand and Japan but got above 30% in Singapore, China 2 and Vietnam.

Overall, prevalence of resistance to the older agents, gentamicin and co-trimoxazole, among all of the isolates of Enterobacter reported from these countries did not appear to increase throughout the nineties, while resistance to the newer fluoroquinolones increased by at least 50%.

**Enterococcus species**

Clinical isolates of enterococci are predominantly Enterococcus faecalis, which are nearly all susceptible to ampicillin, and usually to nitrofurantoin as well. Isolates of Enterococcus faecium are usually resistant to ampicillin and to nitrofurantoin, and so susceptibility testing can be used as a practical means of distinguishing the two species. Only a percent or two of clinical isolates of enterococci had been E. faecium in most of the world, until that percentage began to increase in the last two decades. That increase has been ascribed to an increasing number of nosocomial strains of E. faecium circulating in hospitals at a time where b-lactam antibiotics, such as ampicillin or cephalosporins, have been increasingly used in hospitals.

This trend may still have been ongoing in some of the countries surveyed here through the nineties. Countries that had less than about 15% of their enterococci resistant to ampicillin earlier in the decade, such as Australia, Hong Kong, Japan, Korea, Singapore and Vietnam, tended to have higher percentages resistant later. Those with higher percentages resistant earlier did not appear to increase
further, as though they had already reached some kind of equilibrium. A similar but more erratic trend may be discernable for resistance to nitrofurantoin.

The exception to either of these trends was New Zealand, where resistance to ampicillin remained mostly below 1.5%, and to nitrofurantoin below 2.5%, throughout the decade. It would be interesting to know whether New Zealand’s exemption thus far from what seems a strong trend elsewhere could be ascribed to its antimicrobial usage practices or to its relative isolation from a global epidemic.

Relative isolation from a global epidemic is also an especially pertinent issue for the data here on resistance to vancomycin in enterococci. Vancomycin-resistant enterococci (VRE) were virtually unknown in the world until a little over a decade ago. A few years later they began to appear in the United States and have since become a major nosocomial problem, and a nearly untreatable problem, in many if not most hospitals throughout the U.S.

The major question here is whether VRE have appeared in hospitals of this Region. The data here show small and somewhat variable percentages of resistance to vancomycin in isolates of enterococci. It is known, however, from other experience, that testing for this is difficult, and without very strict quality control false resistance may be reported. It has also been the experience in the U.S. that once VRE have become established in a hospital their prevalence tends to rise soon to levels higher than most of those reported here.

For these reasons, it seems possible that VRE have not yet arrived, or at least have not yet become widespread, in this Region. It is an important question, because early detection of the true arrival of VRE and early focus on containment before it becomes widespread might avert or delay what would otherwise become an enormous and enormously expensive problem.

This is another of the many reasons why linked, common-format electronic database files of patient-level quantitative susceptibility test results at each medical center (as for example with the WHONET software) would make a more effective resistance surveillance system than the country-summarized paper lists of overall percentage-resistant by species that have been collated yearly to produce the gross overview tables being reviewed here.

The database files of quantitative susceptibility test results would permit immediate inspection of the distribution of inhibition zone diameter values of both clinical isolate and internal quality control
test results. This could discriminate borderline readings falsely categorized as resistant from discrete clusters of higher-level resistant strains likely to be true VRE. It could also identify distinctive patterns of co-resistance to agents other than vancomycin that might further distinguish a true outbreak strain. It would then make possible day-to-day tracing of in-hospital locations of patients with such VRE and thus focus efforts to contain them.

**Escherichia coli**

The data on Escherichia coli is divided here into data on urine isolates and data on all other isolates. This review will examine them altogether, but will at the same time look for any appreciable differences between them.

*E. coli* occupy a distinctive niche. They are the most prevalent aerobic species in the colons of humans and other vertebrates, and so also the most common aerobic agent of bowel-related sepsis. The colon’s proximity to urine outflow make *E. coli* in addition the species that most often infects the urinary tract (predominantly of women) and so also the most common cause of urosepsis. Since these infections arise mostly in the community, most of the medically significant isolates of *E. coli* appear to be non-nosocomial.

*E. coli* have almost no intrinsic resistance to antimicrobials, so virtually all of the resistances observed in any strain of *E. coli* were absent from its ancestor of sixty years ago and have gradually accumulated in that strain since.

Resistance of *E. coli* to oral antimicrobial agents widely used to treat *E. coli* for more than three decades, such as tetracycline, ampicillin or co-trimoxazole, has risen slowly over this period, but at different rates in different places. It appears to be still rising, suggesting that it has not reached an equilibrium. Accordingly, in the data here, no country — with the exception of Japan’s approximately 30% — reports much less than 50% resistance to ampicillin among isolates of *E. coli*, and most countries report between 60-80% resistant (see Figure 5). Percents resistant for tetracycline are not quite as high, and have a range from about 30-70%. For co-trimoxazole the range seems wider at 20-80%.
Figure 5. Antimicrobial resistance rates for ampicillin in *Escherichia coli*, 1991-1998.

The much lower rates of resistance among the isolates to *E. coli* to first generation cephalosporins, exemplified by cephalothin, than to ampicillin may be misleading. The same resistance mechanisms (mostly TEM b-lactamases) inactivate both ampicillin and first generation cephalosporins, but with different kinetics. As a result an ampicillin resistant isolate is easy to detect, whereas the same isolate may just miss falling into the resistant category for cephalothin unless tested with a heavy inoculum. The clinical significance of this is not certain, but an *E. coli* that tests resistant to ampicillin should probably not be considered fully susceptible to cephalothin or other first-generation cephalosporins.

The situation is quite different for third generation cephalosporins, exemplified here by cefotaxime. They were not hydrolysed by TEM type b-lactamases, and so nearly all *E. coli*, including all those resistant to ampicillin, were fully susceptible to third generation cephalosporins when they began to be used about twenty years ago. About five years later, however, strains of *Klebsiella* (see below) at first, and then less often strains of *E. coli*, began to be found that were at least moderately resistant to third generation cephalosporins. The b-lactamases in these strains, which had not been able to hydrolyse third-generation cephalosporins earlier, had begun to mutate in ways that extended their hydrolytic substrate spectra to include third generation cephalosporins. These resistance-causing mutant enzymes were called extended-spectrum b-lactamases (ESBLs).

Some countries, such as Australia, Japan and New Zealand, consistently report here less than one percent of *E. coli* resistant to cefotaxime, and so probably have essentially no ESBLs in their isolates.
China and Vietnam report about a fifth of their *E. coli* to be resistant to cefotaxime, and these are likely to have ESBLs. The other countries fall in between.

Resistance to gentamicin and to fluoroquinolones in *E. coli* are interesting for different reasons.

Gentamicin is administered to patients parenterally. For this reason the largely community-origin *E. coli* are not expected to be as much exposed to gentamicin as are more nosocomial strains. This is thought to be the reason why prevalence of resistance to gentamicin in *E. coli* is rare in some parts of the world, as it is (<2%) in this data for Australia and New Zealand. It is slightly higher, but still averaging less than 5% in Japan and Tonga. Fiji, Malaysia and Singapore average around 10%. In Korea, Hong Kong, China and Vietnam, however, a quarter to a half of the isolates of *E. coli* tested resistant to gentamicin (see Figure 6).

There is thus across the Western Pacific Region an approximately 20-fold difference between the prevalence of resistance to gentamicin among isolates of *E. coli* between the two countries with the lowest and the three with highest levels. The large numbers of isolates of this species, moreover, tend to make the percentages for any country relatively consistent from year to year, so that if given the list of percentages for next year without the names of the countries you could probably match many of them to the right country.

**Figure 6. Antimicrobial resistance rates for gentamicin in *Escherichia coli*, 1991-1998.**
It would be easier to explain this very wide country-to-country variation in percentages resistant to gentamicin for a more nosocomial species, such as *Klebsiella*, for which in-hospital use of gentamicin could vary greatly or within which a few plasmids or strains expressing gentamicin resistance genes could circulate widely in intensive care units and be isolated over and over again. It is much harder to explain for *E. coli* if we have the usual assumption that these isolates come from huge reservoirs of *E. coli* in the community that would be rarely exposed to gentamicin and from which the same strain would rarely be isolated twice.

We may have to consider for some countries such possibilities as there being wide exposure to gentamicin in the community or food chain, or the possibility that some multi-resistant strains of *E. coli* have evolved to spread and behave as nosocomial organisms in some countries, even thought that is virtually unknown in other countries. In approaching these problems it would again be useful to have for analysis not just these summarizing lists of aggregated percents resistant but rather the kind of isolate-level databases mentioned above. Such databases would make it possible to explore, for example, whether the isolates are coming from patients in the community or in intensive care units, or whether strains with certain distinctive antibiotic types are being isolated over and over again. These are important questions because they could uncover a major problem for Infection Control or for Food Safety.

An even more important problem can be seen here in the data on fluoroquinolone resistance in *E. coli*. It is important because fluoroquinolones are the last major family of oral antimicrobial agents that still remain effective against most bacterial pathogens. This is a critical role that has been filled successively over the past half century first by tetracyclines and chloramphenicol, then by ampicillin, and then by co-trimoxazole. Each of these agents in its time saved more lives than any other because it could be given by mouth blindly to unhospitalized, undiagnosed, severely ill septic patients in the poorer parts of the world where most people live, and cure most of them. Gradually, growing resistance to each of those earlier agents made them, one after another, largely ineffective in that role.

Fluoroquinolones alone have remained widely effective in that role today, and the persisting low rates of resistance to them in the parts of the world where resistance is most monitored has encouraged optimism, if not complacency, that this will persist.

In this context, the data being reviewed here on resistance to fluoroquinolones in *E. coli* are most disturbing. In Australia and New
Zealand only a percent or less of \textit{E. coli} isolates have tested resistant to fluoroquinolones in any year, which would be comparable to levels observed in the U.S. or parts of Europe. Such levels were reported here for Japan also through 1994, but have been rising since and now exceed 5\%. A comparable rise began a year or two earlier in Malaysia. Much steeper rises over the same period in Vietnam and Hong Kong have led to a quarter or more of those isolates being resistant by 1998.

More rapid rises in prevalence of resistance to fluoroquinolones in \textit{E. coli} must have occurred earlier in Singapore, Korea, and China, because when they first filed such data here in 1992 a third or more of their isolates were already resistant and about half were by 1998. Over the same period \textit{E. coli} from the Philippines have fluctuated between a quarter and a third resistant to fluoroquinolones (see Figure 7).

This means that within this Western Pacific Region there is now as much as a 50-fold variance between countries in prevalence of resistance to fluoroquinolones among clinical isolates of \textit{E. coli}. What makes this even more remarkable is that fluoroquinolones began to be used only about fifteen years ago. At that time there were no known resistant isolates, but by half way between then and now nearly half of the isolates had become resistant in some countries, while all but a percent or less were still susceptible through 1998 in other countries of the Region. This projects to something like a hundredfold difference between those countries in their rates of increase in resistance.

**Figure 7. Antimicrobial resistance rates for fluoroquinolones in \textit{Escherichia coli}, 1991-1998.**
These observations raise much the same questions about their possible causes as did the observations above about between-country variance in rates of resistance to gentamicin among clinical isolates of *E. coli*. The possibilities of some broad exposure to fluoroquinolones in the community, as in the food chain, or the possibility of multi-resistant and quinolone-resistant strains of *E. coli* circulating as nosocomial agents in hospitals are among those that need to be explored. Again, isolate-level databases from each medical center would greatly facilitate such investigations.

It should be emphasized again that fluoroquinolone resistance in *E. coli* is a much more important problem than is gentamicin resistance in *E. coli*. Other parenteral agents remain as effective as gentamicin. Increasing resistance to other agents in major bacterial pathogens, however, has made most other parenteral agents less widely effective, and other oral agents far less widely effective, than the fluoroquinolones have been since their introduction.

### *Haemophilus influenzae*

The isolates are divided into a larger set “isolated from sputum, otitis and sinus”, and a smaller set called “invasive (blood, CSF)”, which would presumably be largely Group B. Roughly a fifth of the isolates in either set tested resistant to ampicillin, without any country-to-country or year-to-year trend apparent, and about that many also tested positive for b-lactamase. Resistance to chloramphenicol fluctuated greatly with most values in or less than single digits, except for Vietnam, which had between a fifth to a half of its isolates in either set resistant to chloramphenicol. Nearly half of the isolates of *H. influenzae* from China, Vietnam and Malaysia, but only 10-25% of those from the other countries, were resistant to co-trimoxazole. Resistance to tetracycline averaged more than ten percent only in Vietnam, where it was closer to twenty percent. Resistance to fluoroquinolones, which are generally not approved for use in children, was not tested.

### *Klebsiella species*

*Klebsiella* species usually consist mostly of *Klebsiella pneumoniae* plus smaller numbers of *Klebsiella oxytoca*.

*Klebsiella* are uniformly resistant to ampicillin because of a genera-specific chromosomal b-lactamase. They have been of particular interest in recent years because they have been the genera in which the newly emerged plasmid-mediated ESBLs have been most prevalent.
An ESBL is the likely mechanism of resistance here in any strain of *Klebsiella* that tests resistant to cefotaxime. Additional strains carrying other ESBLs might also be detected if another third generation cephalosporin, such as ceftazidime, were added to the test panel, since different ESBLs hydrolyze different cephalosporins at different rates.

Using cefotaxime here as a surrogate test for ESBLs, we can estimate from the data that only a few percent of *Klebsiella* isolates carried ESBLs in Australia, Fiji, Japan, Tonga and New Zealand, while more than a third of the isolates did in Singapore and Vietnam (see Figure 8). The Philippines stayed at 12-16% resistant throughout, while Malaysia, Korea and China roughly doubled their percents resistant over the decade, ending at about 25%.

ESBLs, estimated in this way, were about twice as prevalent in the isolates of *Klebsiella* surveyed here as in the isolates of *E. coli*. This preponderance of ESBLs in *Klebsiella* has been observed repeatedly, but often by a greater ratio.

Other comparisons between *Klebsiella* and *E. coli* may be of interest. Overall, about a half of all *E. coli* isolates but only a third of *Klebsiella* isolates were resistant to co-trimoxazole or to tetracycline. Slightly less than a fifth of either were resistant to gentamicin.

**Figure 8. Antimicrobial resistance rates for cefotaxime in *Klebsiella pneumoniae*, 1998.**
About a fifth of the *Klebsiella* in Australia and New Zealand, but half or more everywhere else, were resistant to co-trimoxazole or to tetracycline. Two percent or less of the isolates of *Klebsiella* in New Zealand or Japan, ten percent or less in Australia, Fiji and Tonga, 10-20% in Malaysia, Hong Kong and China, and >30% in China 2, Korea, Singapore, Philippines, and Vietnam were resistant to gentamicin, with no apparent trends over time.

Resistance to fluoroquinolones remained less than 3% throughout the decade in isolates of *Klebsiella* from Australia, New Zealand and Japan, and remained at around 10% in Korea, and at about 25% in Singapore (see Figure 9). However, it roughly doubled, from about 4% to 8% in Malaysia, from 6% to 12% in China 1, from 14% to 27% in China 2, and appeared to have more erratic increases in the Philippines, Hong Kong, and Vietnam. The average percentage of resistance to ciprofloxacin, the only fluoroquinolone tested in 1991, for *Klebsiella* isolates from all of the countries in that year was 3.1. The corresponding percentages for succeeding years when testing was reported for fluoroquinolones was 7.9 and 7.0 for 1992 and 1994, 8.9 and 9.3 for 1995 and 1996, and 13.0 and 14.9 for 1997 and 1998.

It is interesting to compare these overall percentages of resistance to fluoroquinolones for isolates of *Klebsiella* from the Region to the corresponding percentages discussed earlier for *E. coli*. The *E. coli* results, as mentioned earlier, were presented as a larger set for urine isolates (values presented below) and a smaller set for other isolates (presented below in parentheses following urine percentages). For ciprofloxacin in 1991 the *E. coli* percentages were 0.1 (0.1). For fluoroquinolones in succeeding years, the *E. coli* percentages were for 1992 and 1994, 11.4 (6)% and 21.7 (14.3)%, for 1995 and 1996, 20.6 (13.5)% and 27.5 (20.3)%, and for 1997 and 1998, 33.9 (22.2)% and 29.2 (24.2)%. 

It is interesting also, but unexplained, that the percentages in parentheses for the non-urine isolates are consistently lower than, but with the same rising trend as, the non-urine isolates.

To summarize, the overall prevalence for the Region of resistance to fluoroquinolones increased more rapidly, and to levels twice as high, in surveyed isolates of *E. coli* than in surveyed isolates of *Klebsiella*. These observations are not likely to have been affected by testing methods because the conservative breakpoints generally used for testing fluoroquinolones make false resistance unlikely, and because use of the same methods and reagents concurrently for both types of isolates further ensures comparability.

We might have expected the opposite of what we find here. If strains of *Klebsiella* recirculate nosocomially in hospital intensive care units, as has often been seen, acquisition of resistance by a few such strains, repeatedly exposed to antimicrobials and then repeatedly cultured from different patients, the percent of total *Klebsiella* isolates that are resistant could increase rapidly. If there is a reservoir of innumerable *E. coli* strains in the community, in contrast, it might be expected to take a longer time for an appreciable percentage of those strains to encounter an agent and acquire resistance to it.

The rates of acquisition of fluoroquinolone resistance in *E. coli* and in *Klebsiella* seen in many countries of this Region thus challenge these expectations. They suggest that *E. coli* strains here either
mutate to resistance sooner or circulate nosocomially in hospitals, or that exposure to fluoroquinolones in the community, food chain or environment is for some reason greater than elsewhere.

**Moraxella (Branhamella) catarrhalis**

Isolates of *Moraxella catarrhalis* from most of the countries in the Region are, as expected, predominantly (approximately 90%) resistant to ampicillin with comparable percentages β-lactamase positive. Exceptions exist for Fiji, Malaysia, Philippines and Vietnam, however, where only a third or fewer of the isolates are resistant to ampicillin. Malaysia and Vietnam also differ in having a quarter or more of their isolates resistant to tetracycline or erythromycin. Retesting such exceptional isolates in different laboratories might be the best way to begin evaluation of their significance.

**Proteus mirabilis**

About 15% of the isolates of *Proteus mirabilis* from Australia, New Zealand or Japan, but nearly half or more of those from other countries in the Region, are resistant to ampicillin. Roughly the same relationships hold for resistance to chloramphenicol or to co-trimoxazole. Resistance to gentamicin is less than 2% in Australia, New Zealand and Japan, and ranges from about 7-30% for the others. Less than a percent are resistant to fluoroquinolones in Australia and New Zealand, and only China 2 of the other countries exceeds 10%. Only China 1 and the Philippines consistently approach 10% resistant to cefotaxime. Most isolates are, as expected, resistant to tetracycline.

**Proteus vulgaris**

Most of the isolates of *Proteus vulgaris* are resistant to ampicillin and to cephalothin. Resistance to cefotaxime fluctuates, but exceeds 20% some years in Australia, China, Japan, New Zealand, Philippines and Vietnam. More than a quarter of the isolates are resistant to chloramphenicol in most countries, but resistance to gentamicin consistently exceeds 10% only in the Philippines, Fiji, China and Vietnam. Resistance to fluoroquinolones approaches or exceeds 10% some years in China, Malaysia, Philippines and Vietnam.
Providencia species

Most of the isolates of Providencia species are resistant to ampicillin, cephalothin, amoxicillin/clavulanic acid and chloramphenicol. Resistance to cefotaxime is erratic from year to year but reaches 10% in at least one year in every country but Hong Kong and Korea, and exceeds 20% in China, Philippines and Vietnam. Resistance to gentamicin exceeds 25% some years in every country except Malaysia and Tonga. Resistance to fluoroquinolones reaches 20% at least one year in every country except Malaysia and New Zealand.

Pseudomonas aeruginosa

Since antimicrobial agents began to be used sixty year ago they have been known to select for the overgrowth of Pseudomonas aeruginosa, especially in respiratory and other sites of hospitalized patients. Initially, this was because P. aeruginosa had intrinsic resistance to the earlier agents, but they proved later to have some resistance to newer agents as well, plus the ability to develop more resistance quickly. Their treatment has thus depended on their fluctuating susceptibility at any place to a small number of mostly parenteral antimicrobial agents. These include, among those tested here, the aminoglycosides (gentamicin, tobramycin, netilmicin and amikacin), ticarcillin and piperacillin, ceftazidime, and, as the sole oral agents, the fluoroquinolones.

The aminoglycoside family of antibiotics are extensively used for treatment of Pseudomonas, although the concentrations that they reach in respiratory tissues are thought to be only marginal. Within the aminoglycoside family, gentamicin has been the least expensive and the most widely available and used. Isolates of P. aeruginosa are expected to test susceptible to tobramycin slightly more often and to netilmicin slightly less often than they do to gentamicin. That is reflected in the data here, in which overall average percentage resistant for all isolates of P. aeruginosa from the Region was for gentamicin 28.6%, for tobramycin 24%, and for netilmicin 36.7. There was considerable fluctuation in percentage resistant to these agents from year-to-year in some countries, perhaps representing shifts of nosocomial strains, but no appreciable trend over the decade.

Percentage of P. aeruginosa resistant to gentamicin fell within or close to the 25%-35% range for half of the countries. It was approximately 10% for Australia and New Zealand, 15% for Hong Kong and Japan, and 50% for Korea, Philippines and Vietnam.
Amikacin is considered somewhat separate from the other aminoglycosides because it is not inactivated by the resistance mechanisms that inactivate them, but by others that have emerged to inactivate it. Perhaps because it has been expensive and less used and its special resistance mechanisms therefore less selected for, there is usually less resistance to it than to the other aminoglycosides in most species of bacteria. This has been true, although not explicitly commented upon, for other species in this data set, and is true here also for isolates of *P. aeruginosa* from the Region which average overall only 11.9% percent resistant to amikacin.

Resistance to amikacin among tested isolates of *P. aeruginosa* rarely exceeded 10% in any of the countries of the Region except Philippines and Korea, where it was in the 20%-30% range. Since these were also two of the three countries with the higher percentages of *P. aeruginosa* resistant to gentamicin, it raises the question of whether high prevalence of gentamicin resistance prompted more use of amikacin leading to more resistance to amikacin. Concern about such a cycle of events, along with the expense of amikacin, has caused amikacin to be reserved for only very selective use in some countries.

Resistance among isolates of *Pseudomonas aeruginosa* to the β-lactam antibiotic piperacillin, and to the related carbenicillin in countries where it was tested, exceeded 10% in some years in all countries, but rarely exceeded 25% except in Philippines and Korea where it approximated 35% and 50% respectively.

Overall resistance to the anti-pseudomonal cephalosporin, ceftazidime, among all of the isolates of *Pseudomonas aeruginosa* surveyed from the Region increased slightly over the decade from just under 13% for 1991 through 1994 to 17% for 1996-1998. It had a relatively narrow range from about 5% resistant in New Zealand and 7% in Australia to a high of around 25% in Philippines and China, with outlying values exceeding 50% only in Vietnam.

Overall resistance to fluoroquinolones among all of the isolates of *Pseudomonas aeruginosa* from the Region increased more steeply from slightly over 16% in 1992 and 1994 to just under 23% in 1996-1998. The countries with the least resistance, Australia and New Zealand each reached 13%, and only Philippines and China exceeded 25%, except for outlying Korea, which ranged from 41% to 58%.

In considering such resistance in *Pseudomonas*, or in any other species where there is frequent multi-resistance, it is important to keep in mind the linkage in strains of resistance to different
antimicrobial agents. If resistance were distributed randomly in strains of bacteria there would rarely be a strain resistant to most or all of the agents. It is, however, rarely random but often closely linked. As a consequence, as percentages resistant to different agents increase, there will be a growing proportion of strains resistant to all or nearly all of the agents, and therapeutic options for many patients will diminish or disappear. This is an important dimension of the resistance problem that needs to be monitored for optimal resistance management, and another reason for isolate-level databases that would allow such monitoring.

**Salmonella non-typhi, non paratyphi A**

Most of the countries submitted susceptibility test results on from one to several hundred of these isolates each year, probably representing many different serotypes. Serotype data, where available or where it could be developed for special studies, would be useful because it would allow detection and tracing in the Region of multi-resistant serotypes recently shown to be a problem in other parts of the world, such as *Salmonella typhimurium* DT104.

Resistance levels vary widely from year-to-year and country-to-country, as might be expected from multiple small outbreaks of different serotypes with different resistance patterns. Overall, less than a fifth of the isolates from the whole Region tested resistant to ampicillin, and somewhat fewer to chloramphenicol and co-trimoxazole, with higher percentages reported in some years from Philippines, Korea, Hong Kong and China. A percent or two on average were reported resistant to fluoroquinolones, with no apparent clustering in year or country.

Small numbers of isolates resistant to cefotaxime in China, Philippines, New Zealand, Singapore and Vietnam should be further investigated, because ESBL-carrying strains of

Non-typhi, non-paratyphi *Salmonella* have now been identified as causes of serious outbreaks in other parts of the world, at least one nosocomial in multiple neonatal units.

**Salmonella paratyphi A**

Double digit but only rarely triple digit numbers of isolates were reported from most countries most years. Only a few isolates were reported resistant to any of the antimicrobials in occasional years.
**Salmonella typhi**

Appreciable numbers of isolates of this major pathogen were reported, especially from Malaysia (up to 300 per year), Vietnam (up to 500 per year), and Philippines (up to 700 per year). Malaysia, Philippines, Singapore and several other countries report around a tenth of their isolates resistant to ampicillin or chloramphenicol or co-trimoxazole, raising the possibility that many of these might be the *S. typhi* strains resistant to all three that have been a problem in parts of Asia for the last decade. That would certainly seem likely for Singapore where the percents resistant to these three agents have been identical in the last three recorded years, culminating in 35.7% for the 42 isolates tested in 1998. It has to be true for the 600 or so yearly isolates in Vietnam, which have tested around 90% resistant to each of those three agents in recent years.

Confirmative studies need to be done on the few isolates of *S. typhi* that have tested resistant to fluoroquinolones in each of the last several years, but not in earlier years, in China, Philippines and Vietnam. Reduced levels of susceptibility, but not resistance, to fluoroquinolones have been reported in India and associated with slower response to fluoroquinolone therapy. The emergence of full resistance in one of the multi-resistant strains of *S. typhi* would have the potential for catastrophe.

**Shigella species**

Only a few isolates of *S. boydii* or of *S. dysenteriae* are reported from some countries in some years. China reports 500 or more isolates of *S. flexneri* annually, Hong Kong around 100, and most of the other countries double-digits in most years. Most countries report double-digit numbers of isolates of *S. sonnei* yearly and occasionally more than a hundred.

Most of the isolates of *S. flexneri* from most of the countries are resistant to ampicillin, and perhaps slightly fewer to tetracycline, chloramphenicol and co-trimoxazole. China, Hong Kong, New Zealand, Philippines and Vietnam have each reported small numbers of isolates resistant to fluoroquinolones, and these too should probably not be recorded without being further examined.

The isolates of *S. sonnei* and the few of *S. boydii* and *S. dysenteriae* were slightly less often resistant to ampicillin, chloramphenicol or co-trimoxazole than were the isolates of *S. flexneri*. 
A comparison of the very different experiences of Tonga and Fiji with respect to *S. flexneri* is particularly interesting (see Figure 10). Data suggest that the resistance situation in Tonga has been relatively stable. A bi-resistant strain (ampicillin and co-trimoxazole) persists at >90% prevalence. In contrast, Fiji began the decade mostly with strains susceptible to all four antimicrobials tested, and the subsequent rapid emergence of tri-resistant strains (ampicillin, chloramphenicol, and tetracycline), susceptible only to co-trimoxazole.

**Figure 10. Antimicrobial resistance rates for *Shigella flexneri* in Tonga and Fiji, 1994-1998.**

*Serratia* species

Strains of *Serratia* species, probably mostly *Serratia marcescens*, are usually nosocomial. They were isolated in the data reviewed here several-fold less often than other Gram-negative bacilli likely to be nosocomial, such as *Klebsiella*, *Enterobacter* and *Serratia*, and five to ten-fold less often than *Pseudomonas*. *Serratia* have intrinsic resistance to ampicillin and first generation cephalosporins, as seen in the test results here, ascribed to an inducible ampC type chromosomal ß-lactamase. This usually also expresses resistance to cefotaxime by test in about a fifth of the isolates, as is seen somewhat erratically in the results here. They also have intrinsic moderate-level resistance to tetracycline, which some of the laboratories here reported in only about half of the isolates.
They average here, overall, about 10% resistant to fluoroquinolones, 20% to gentamicin, and 35-40% to chloramphenicol, with no apparent trends over the time observed. They were 50-60% resistant to chloramphenicol among samples of 250-500 isolates/year over the four years they were tested in Australia.

**Staphylococcus aureus**

Isolates of *Staphylococcus aureus* were, after *E. coli*, the second most frequently tested in the data from the Region. Methicillin-resistant *S. aureus* (MRSA) averaged, overall, 22.2% of all *S. aureus* isolates in 1991, 1992, and 1994, and 31.5% in 1995 through 1998, although not all countries tested the combination in 1991 and 1992. Percent resistance to penicillin remained between 85.7% and 91% throughout.

Only about one percent of tens of thousands of isolates of *S. aureus* tested yearly in New Zealand were MRSA until 1995 when it increased abruptly to 4.1%, and then gradually to 4.9% for 1998. Methicillin resistance in Fiji ranged from 5-8%, and in Philippines and Vietnam from 15-19%, until 1998 when Vietnam reported 29.5% resistant among 500 isolates tested.

Among tens of thousands of *S. aureus* isolates sampled yearly in Australia, an average of 20.4% were MRSA in 1992 and 1994, but this had risen to 24.7% in 1995 and 1996, the last years for which data are available. Similarly, among yearly samples of several thousand *S. aureus* in Malaysia, an average of 24.2% were MRSA in 1991, 1992 and 1994, but this had risen to 34.2% in 1995-1998 (see Figure 11).

Approximately a third to a half of the isolates of *S. aureus* reported from Hong Kong and in China 1 over the decade were MRSA, with fluctuations too great to display any trend. Among samples averaging about a thousand *S. aureus* yearly for China 2, and several thousand yearly for Korea and Japan, each reporting for only three or four years, half to three quarters on average were MRSA.

The overall impression is that at the beginning of the decade there may have been a nearly fifty-fold difference between the prevalence of MRSA in different countries in the Region and that this ratio has since diminished as the prevalence of MRSA has increased in countries where it had been lower but not apparently in countries where it had been very high.
The tendency of MRSA to persist in or on any given patient makes it especially subject to being isolated repeatedly from the same patient, and we do not know to what extent such repeat isolates may or may not have been excluded from these data. Possible over-reporting due to such repeat culturing, however, would not seem sufficient to alter the trends toward greater prevalence seen here in countries where it was initially low, and certainly not the very large country-to-country differences.

Another minor point is the use of methicillin as the test disk in these surveys. NCCLS has suggested using oxacillin to test for \( \beta \)-lactam resistance in staphylococcal because of some evidence that it deteriorates more slowly in storage than does methicillin.

The \( \textit{mec} \) gene products of MRSA make them resistant to other \( \beta \)-lactam antibiotics besides methicillin. In addition, resistance to other antimicrobial agents also tends to be clustered in MRSA, often leaving most other strains of \( S. \textit{aureus} \) resistant only to penicillin and ampicillin because of their penicillinase. This seems to be reflected here in that the prevalence of resistance to most of the other agents in any country seems to approximate the prevalence of resistance to methicillin in that country.

Such linkage would be particularly interesting to examine for resistance to fluoroquinolones, which has been observed to increase rapidly in strains of MRSA as they begin to become prevalent, but very little in other strains of \( S. \textit{aureus} \). Without a database to examine such linkages of resistance in MRSA as compared to other \( S. \textit{aureus} \),
however, there are probably not useful ways to analyze resistance to these other agents in *S. aureus*.

**Staphylococcus coagulase negative – blood isolates**

Most countries reported between several hundred to occasionally a thousand or more blood isolates of coagulase-negative staphylococci each year. Overall, on average, slightly under half of these isolates were reported as resistant to methicillin and 75-80% as resistant to penicillin.

Test reports of susceptibility to methicillin or oxacillin among coagulase-negative staphylococci have been considered unreliable in the past. Recently, however, investigations have led to new and more stringent interpretation breakpoints that will categorize fewer isolates as susceptible but support those then as being truly susceptible. To the extent that countries have kept zone diameter test measurements in databases, instead of just interpretive categories, it would be possible to go back and analyse the original data with these new and better-standardized breakpoints.

The special value of a reliable test for identifying strains of coagulase-negative staphylococci that are truly susceptible to methicillin or oxacillin is that it will permit treatment of infection due to those strains, commonly line-related sepsis, with something other than vancomycin. Vancomycin has been used nearly universally and by default for such infections because of the suspected unreliability of tests using the former breakpoints. That something else could be oxacillin, but non-β-lactam antimicrobials might also be used in some circumstances because, as with *S. aureus*, much of the resistance to those other agents appears to be found mostly in the methicillin-resistant strains.

Prevalence of resistance to those non-β-lactam antimicrobials among the isolates here appears variable from year-to-year, but then not highly varied from country-to-country.

This may reflect, again, the clustering of resistance to those antimicrobials in the β-lactam-resistant strains. Interestingly, among the lowest and seemingly most erratic percentages of resistance for any of these agents is resistance to fluoroquinolones. This could be consistent with the β-lactam resistant strains of coagulase negative staphylococci becoming resistant to fluoroquinolones sooner than the susceptible strains, as the MRSA have done. Analyses of such linkages in databases with inhibition zone measurements could delineate them in relation to the new oxacillin breakpoints.
Staphylococcus saprophyticus

Isolates of *Staphylococcus saprophyticus*, which causes occasional urinary tract infections of women in the community, are reported here in samples of less than a hundred from most countries in most years, with more than a thousand from New Zealand in some years. About a third, overall, test resistant to methicillin, two thirds to penicillin, and about a quarter to co-trimoxazole or tetracycline. Year-to-year variance makes country-to-country differences difficult to discern. An exception is New Zealand, which, with the stability of its large sample base, appears to have only about ten percent of its isolates resistant to most of the non-β-lactam antimicrobials, and only a percent or two resistant to fluoroquinolones.

Streptococcus pneumoniae

*Streptococcus pneumoniae* is the major pathogen for acute morbidity and mortality in respiratory infection. Isolates of *S. pneumoniae* are divided in the data here into invasive isolates (isolated from blood and CSF) and respiratory isolates (isolated from sputum, ear, eye, and sinus). These two groups together have close to a hundred or more isolates from most countries most years. They are reviewed together here, but scanned for differences.

Averaged together, the isolates in both groups from all of the countries in the Region show substantial increases in resistance to all of the antimicrobial agents tested over the eight years (1991-1998) of observation.

Resistance to penicillin is probably of greatest interest. Growing levels of resistance to penicillin over the past decade in regions of the world where such resistance had not been seen before have caused treatment of meningitis to fail and are complicating treatment of pneumonia.

Data on pneumococcal resistance to penicillin does, however, raise questions of testing methodology. Because pneumococci had been so exquisitely susceptible to penicillin, the levels of resistance that begin to cause clinical problems are still relatively low when compared to levels of resistance to other agents, and these levels have thus been somewhat difficult to measure reliably. Standard methods for such testing have been worked out over the decade, but without further inquiry we cannot know which of these methods came into use when in the laboratories testing the isolates that are surveyed here.
In spite of this concern, features of the data reinforce the impression that there has been a true and substantial increase in resistance to penicillin among pneumococci of the Region (see Figure 12). Although the small numbers make it irregular, percent of both invasive and respiratory isolates reported resistant to penicillin rose in most countries over the years surveyed. This is supported by a similar rise in resistance to erythromycin, since penicillin-resistant pneumococci are more often resistant to erythromycin.

Figure 12. Antimicrobial resistance rates for oxacillin or penicillin in *Streptococcus pneumoniae*, 1991-1998.

**Vibrio cholerae**

Scattered isolates from most countries are too few to establish trends, except for Philippines, which report on the order of five hundred per year. Percents resistant to any agent there remain in the low single digits, suggesting that any strain testing resistant to any agent should be carefully retested for confirmation.
RECOMMENDATIONS

This Report reviews and summarises data from the past decade of the WPRO Programme for Surveillance of Antimicrobial Resistance. Accordingly, the recommendations of this Report focus principally on ways to strengthen surveillance and increase its role in the containment of resistance in the Region.

The data reviewed for the Report, however, reveal many serious problems and worsening trends in antimicrobial resistance in various nations of the Region. Control of such problems needs, besides surveillance, implementation of recommendations for many segments of government and society, including patients and the general community.

Developed in collaboration with many experts and partners, the WHO Global Strategy for Containment of Antimicrobial Resistance [5] recommends many practical intersectoral interventions to be taken at local, national, regional, and worldwide levels for improving use of antimicrobials, for limiting the spread of resistant organisms, for promoting new drug development, and for investigating alternative strategies for managing infections with resistant organisms.

This Report will therefore develop recommendations for surveillance of resistance that are consistent with the WHO Global Strategy but in more detail and with more focus on the problems revealed in the data from this Region. The Report will then generally refer to WHO Global Strategy for issues not directly related to surveillance.

1. Public health agencies and patient caregivers, individually and through their institutions and professional societies, should expand and integrate at all levels their efforts to control antimicrobial resistance.

Antimicrobial resistance is an unusually diffuse public health problem. It involves not just one kind of disease but all kinds of bacterial infections and all the healthy humans and animals who carry and spread resistant bacteria. It is unusual also
because it arose from and is made worse each day by health caregivers and others using antimicrobials.

Resistance is thus a major public health problem with both its causes and its remedies peculiarly rooted in the activities of those caring for individual patients. Caregivers give patients antimicrobials as clinicians and pharmacists, isolate patients as infection control workers and produce the data about resistance as microbiologists culturing patients.

Those caregivers greatly outnumber public health workers and are much closer to this major public health problem. Yet, in caring for their patients they rarely see themselves as public health workers managing antimicrobial resistance, while public health agencies can not intervene in all the details of care that constitute management of resistance.

The problem thus seems to require an unusual degree of co-operation at all levels between caregivers and public health workers. Caregivers alone may lack a resistance management program or the means to develop one. Public health workers alone may lack skills needed by such a program and are too few and not in position to carry it out.

This recommendation for better co-ordination of the activities of public health agencies and caregivers is general but will underlie each specific recommendation. It is reflected in the recommendation (5.1) of the WHO Global Strategy that each nation create a National Intersectoral (composed of both) Task Force to oversee control of resistance.

2. **Nations should designate or develop reference microbiology laboratory facilities to co-ordinate, surveillance of antimicrobial resistance in communities, hospitals and other health care facilities by performing the functions listed below.**

   This is essentially recommendation 5.13 of the WHO Global Strategy. It is addressed to National Governments and Health Systems. Some nations may need to develop such laboratories anew. Others may designate existing qualified laboratories, but those will need further support and development to carry out new functions listed below.
A. Recruit clinical laboratories to participate in a surveillance network.

This can be seen as the first step in assisting a group providing care to individual patients, here microbiologists, to derive more public health output from their work. In some nations caregivers may have already organized such surveillance networks, but those networks can be enhanced by reference laboratory functions and support.

B. Assist network laboratories in setting up and using surveillance software.

A reference laboratory needs a computer-experienced person, at least part-time, to help network laboratories set up and fully utilize existing surveillance software and install upgrades as they become available. That person can also serve as the data manager, maintaining the network database and assisting with its ongoing analysis.

C. Support and require routine quality control testing in network laboratories.

Internal quality control is repetitive (e.g. weekly) testing of a set of standard strains. External quality control or proficiency testing is testing of unknown challenge strains sent periodically (e.g. quarterly) to each laboratory by the reference laboratory or other agency. All test measurements are recorded in the databases for later analyses.

D. Develop continuous quality improvement programs for network laboratories.

Continuous quality improvement involves ongoing collegial review by all participants of variances in testing results, which can be monitored in the network databases. This has been done in periodic workshops for participants but may now be also internet-based. It allows for both self-correction and targeted educational interventions.

E. Extend continuous quality improvement to total management of resistance.

Variances seen in network databases reflect not only differences in testing but also place-to-place differences in resistance problems. Growing data and collegiality in a network and parallel development of local management teams (see below) will allow the quality improvement process to extend to other aspects of resistance management.
F. Extend the scope of the databases when newer software allows it.

Existing software files patients’ laboratory results. Newer software may configure analyses to better meet the needs of infection control or may capture data on usage of antimicrobials overall or by patient. Such improvements would enhance the analysis and management of resistance problems at both the local and national levels.

G. Encourage and support selected special studies.

Tests of routine clinical bacterial isolates provide most of the data for surveillance of resistance. The data are free and abundant and have many practical uses in managing resistance, but also limitations. They lack defined denominators and reflect varied sampling and, from some sites, an uncertain mix of infecting and colonizing strains.

Special studies may complement and calibrate routine data, especially if linked to it. Resistance in clinical isolates of *E. coli*, for example, can be compared with that of fecal *E. coli* from untreated people in the same community. Adding additional fields of data to routine files allows additional analyses, as for estimating burden of disease.

Monitoring antimicrobial use in hospitals and the communities they serve and linking those findings to resistance data would be extremely valuable. At present this would probably be at most centers a special study. Software to capture data on antimicrobial use by patient could make this a routine and powerful tool for managing resistance.

3. Hospitals should provide, and their caregivers should utilize appropriately, microbiology services matched to the level of the hospital (e.g. secondary, tertiary), and their susceptibility test reports should be filed in a database that can be queried readily to guide treatment and ongoing local management of resistance.

This recommendation incorporates surveillance–related components of the recommendations for hospitals (Cluster 3) of the *WHO Global Strategy* document. It includes the elements below, which involve both patient care and public health considerations.
A. Provide microbiology services matched to the level of the hospital.

The quality of microbiology services is essential to every other recommendation. It requires workers skilled in the special methods of microbiology and oversight that is alert to new developments and focused on both the needs of patients and the local management of resistance. In many places it will need more training and support.

B. Ensure that caregivers utilize those services fully and appropriately.

Microbiology services are a valuable resource that need to be used at the right times (e.g. before antimicrobial treatment) for those specimens and those patients from which they will yield the most useful information. Disincentives to their use, such as understaffing, delay in reporting or high cost to the patient, need to be minimized.

C. File antimicrobial susceptibility test reports in a database for local querying.

The laboratory’s report on the susceptibility of an isolate from a patient has fields of data on the patient (identity, age, sex, location, date and site of culture) and the isolate (species and measurements of susceptibility). Information for resistance management is in the interrelationships between data in those fields in the files of all the isolates.

For example, the distributions of resistance to different agents or combinations of agents among different species of isolates from different culture sites at different locations in the hospital or community at different times will guide clinicians empirical therapy and infection control’s targeting and evaluation of interventions.

Queried in different ways and compared (benchmarking) with similar analyses from other hospitals the databases may reveal hospital-to-hospital variances in testing, in usage of cultures by different clinical services, in resistance to certain agents or an excess of certain resistance phenotypes, all of which might prompt corrective actions.

WHO makes available to laboratories at no charge software designed for these purposes called WHONET. It also offers a program called BacLink designed to facilitate translations from computerized laboratory reporting systems, which usually lack analytical capability, to WHONET or other analytical systems.
4. Hospitals should establish antimicrobial resistance management teams (ARMs) to co-ordinate the different skills needed to fully utilize local surveillance data for total local management of resistance.

This recommendation is similar to but differs slightly from the recommendations 3.1 – 3.4 of the WHO Global Strategy.

The WHO Global Strategy recommends establishing Infection Control Programmes with responsibility for effective management of antimicrobial resistance in hospitals (3.1) and also effective Hospital Therapeutics Committees with responsibility for oversight of antimicrobial use in hospitals (3.2).

This is modified here to emphasize the value of co-ordinating their efforts, which are closely interrelated. Antimicrobial agents need to be selected with detailed information about the current resistance problems in the hospital, and Infection Control needs to know in detail about the use of the agents driving the problems they are trying to contain.

Each of these committees does have other responsibilities, but it would seem helpful for them to function and see themselves as a team in their efforts to manage antimicrobial resistance. Those teams also need microbiologists and caregivers experienced in other aspects of the problem, such as clinicians and especially infectious disease consultants.

Recommendations 3.3 and 3.4 of the WHO Global Strategy specify additional functions for such a team including developing and updating hospital antimicrobial formularies and guidelines for antimicrobial treatment and prophylaxis, as well as monitoring and informing prescribers about antimicrobial usage.
REFERENCES


