

## Introduction

Sir Alexander Fleming discovered the first antibiotic, penicillin, in 1929. Development of penicillin was given high priority as part of the effort in World War II, and penicillin became widely used after the war. Resistant bacteria arose almost immediately. Not only are resistant bacteria still a problem with the penicillins, but they are a problem or potential problem with all antibiotics. Even daily newspapers and TV shows now carry stories about resistant bacteria. As a sales representative for antibiotics, you should understand bacterial resistance and how it affects physician treatment decisions.

[CALLOUT] Doctors are more concerned than ever about bacterial resistance to antibiotics. As a sales representative, you can expect to receive many questions about resistance.

Resistant pathogens can be a major problem. Consider *Streptococcus pneumoniae*, for instance. When doctors first used penicillin widely in the 1940s, pneumococcal isolates were extremely **susceptible** to penicillin. Pneumonia caused by *S. pneumoniae* could be cured easily by quite small doses of penicillin.

In the 1960s, *S. pneumoniae* with **intermediate susceptibility** to penicillin began to be isolated in various parts of the world. In the 1970s, **resistant** strains were isolated. Resistant strains of *S. pneumoniae* amount to upwards of 45% of isolates in some countries. Resistance can vary by geographic location. For example, in the U.S. in 1991 and 1992, intermediately susceptible or resistant strains were almost 7% of all strains nationwide, but 20% of the strains in Dallas, Texas, were resistant. The magnitude of the potential problem in this country is underscored by the estimated 5,000 cases of meningitis, 500,000 cases of pneumonia, and 6 million cases of otitis media caused by *S. pneumoniae* each year.<sup>1</sup>

[CALLOUT] Doctors will be aware of specific problems with bacterial resistance to antibiotics in their practice area and hospitals. As a sales representative, you should also be aware of the local patterns of resistance.

*Hemophilus influenzae* produces **beta-lactamase** strains that are of increasing concern. Up to 30% of *H. influenzae* strains produce beta-lactamase enzymes, creating resistance to antibiotics that are beta-lactamase susceptible.<sup>2</sup> In the U.S., *H. influenzae* accounts for 50% of cases of acute exacerbation of chronic bronchitis,<sup>3</sup> and 27% of cases of acute maxillary sinusitis.<sup>4</sup>

In selecting and using an antibiotic, the physician must keep in mind the problem of resistance. It is important not only to avoid having resistant bacteria develop in

the patient being treated, but also to keep from increasing the prevalence of resistant pathogens in the community.

**Resistance** has two different meanings in the context of infections:

- Host resistance: A host with a compromised immune system may be more susceptible to infection than a normal person is. Infection arises when the host is unable to combat successfully the entry of a few bacterial pathogens, which can multiply and cause disease.

Some organs or tissues in a host may be susceptible to infection by a certain pathogen, while other organs or tissues in the same individual may be resistant to that pathogen. Some bacteria, *S. pneumoniae* for instance, infect the lungs, causing pneumonia, more often than they infect other organs.

- Bacterial resistance: In this module, resistance refers to the relative susceptibility of a pathogenic microorganism to an antibiotic. A pathogen that is not susceptible to a given antibiotic is said to be resistant to that antibiotic.

## How antibiotics work

To understand the mechanisms of bacterial resistance to antibiotics, it will be necessary to review four of the major actions of antibiotics.

### ***Interference with synthesis of bacterial cell walls***

Production of certain components of the bacterial cell wall is inhibited by the penicillins and cephalosporins. These antibiotics are effective against microorganisms that are multiplying, because they interfere with **cell wall synthesis**. Without a cell wall, bacteria absorb water, swell, burst, and die. Atypical bacteria without cell walls, like *Mycoplasma pneumoniae*, are unaffected by the penicillins and cephalosporins. The same is true of all animal and human cells, for they do not have cell walls.

### ***Interference with protein synthesis***

Bacteria contain **ribosomes**, on which proteins are synthesized. Ribosomes consist of 30S and 50S subunits. Antibiotics of the macrolide group bind to the 50S subunits of ribosomes and block **protein synthesis**. Without new proteins, bacteria cannot grow. Macrolides cannot bind to human ribosomes, which do not have 50S subunits. Therefore, macrolides do not affect protein synthesis in the human host. Because their action does not involve the cell wall, macrolides may

be effective against pathogens that lack cell walls, such as *M. pneumoniae*, and against microorganisms that have developed resistance to penicillins or cephalosporins.

### ***Interference with nucleic acid synthesis***

Other classes of antibiotics, such as the quinolones (and fluoroquinolones), interfere with synthesis of the bacterial **chromosome** during division. In particular, the quinolones interfere with the action of an enzyme, called DNA gyrase. This enzyme uncoils bacterial DNA before the DNA is replicated, and coils it again after replication. Human cells use a different mechanism for DNA synthesis, so their cell division is not blocked by these antibiotics.

[CALLOUT] Some of the quinolones include Cipro® (Bayer Pharmaceutical), Floxin® (McNeil), and Noroxin® (Merck).