# Antimicrobial Resistance

# in *Streptococcus pneumoniae*:

# (Can Vaccination Stop Its Spread?)

Internal Medicine Grand Rounds

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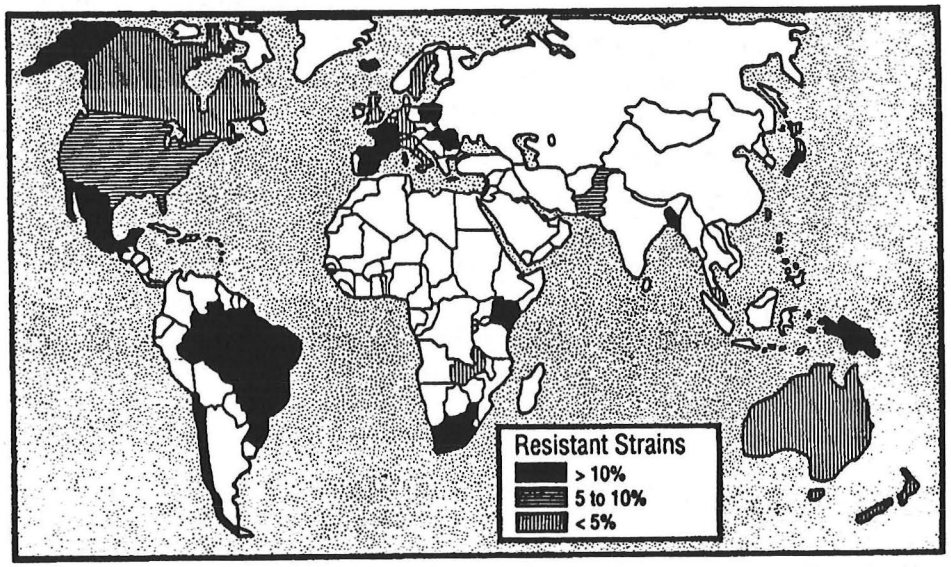
*Streptococcus pneumoniae* is the most common etiologic agent of bacterial pneumonia and meningitis. It was the focus of a great deal of research during the first 40 years of this century, when therapy was relatively ineffective and hospitalized pneumonia patients were common. After the advent of penicillin G in the 1940's, interest in the pneumococcus declined, so that relatively little basic research on the organism was done. Now *S. pneumoniae* once again demands our attention, as antibiotic-resistant strains are causing serious disease in many areas of the world, including Dallas.

Penicillin-resistant strains of *S. pneumoniae* were first reported in isolated instances from Boston, Australia, and New Guinea in the 1960's (1). In 1977, penicillin-resistant pneumococci began to appear in children hospitalized in Durban, South Africa. All of the isolates were highly resistant to penicillin; some were also resistant to other antimicrobials (2). Gradual spread of resistant pneumococci occurred in South Africa, so that cases of disease caused by these organisms are now community-acquired and occur in adults as well as children. In one recent survey, 14.4% of the CSF and blood isolates tested in South Africa were resistant to penicillin (3).

A similar pattern of spread has occurred in other countries, particularly in Spain and in Eastern Europe. This map shows the prevalence and distribution of penicillin-resistant *S. pneumoniae* in 1991 (from Appelbaum (1)).




Penicillin-resistant pneumococci have been isolated from most regions of the U.S. (4). In 1987, 3.6% of isolates received for testing at the C.D.C. were moderately resistant (none was highly resistant). In 1991 and 1992, almost 7% of a similar collection of isolates were resistant to penicillin (1.3% were highly resistant)(R. Breiman, CDC, unpublished data). During the period from 1979 to 1987, the southwestern U.S. had the highest percentage of resistant isolates, 9.6% (4). The most commonly isolated serotypes had the highest frequency of penicillin resistance.

In Oklahoma City, antimicrobial-resistant organisms caused 19% of the cases of invasive pneumococcal disease in 1989-1990 (5). Eight percent were relatively resistant and 1.4% were highly resistant to penicillin. Of nasopharyngeal cultures taken from children with otitis media in Nashville, TN, 32% were penicillin-resistant (6).

Resistant pneumococci have also been found in Dallas. Whereas in the early 1980's, 8% of the isolates from blood, CSF, or middle ear fluid from children at Children's Medical Center were resistant to penicillin, by 1991-2 this percentage was 11.6%. In 1993, 18.5% of the isolates were resistant to penicillin, and 12.9% were resistant to cephalosporins (G.H. McCracken, Jr., personal communication). At Parkland Memorial Hospital, resistant isolates were not noted before November, 1993, when the first was detected; in December, 1993, and January, 1994, there were 3 resistant isolates each month from adult patients. At Zale-Lipshy Hospital, from October, 1993, to January, 1994, there were 3 resistant isolates, 2 of which were highly resistant.

A recent outbreak in children illustrates the potential impact of this phenomenon (7). In 1992-93, penicillin-resistance was noted in 28% of 85 *S. pneumoniae* isolates obtained from middle-ear fluid of children with acute otitis media in a small community in central Kentucky. Forty-five percent of these isolates were highly resistant to penicillin. Penicillin resistance was found in pneumococci from 61% of nasopharyngeal swab cultures obtained from children attending a day care center in the community, and in 33% of cultures obtained from children visiting the county health department. Of the resistant isolates, 65% were highly resistant to penicillin and 27% were resistant to cefotaxime. Moreover, 43% were resistant to erythromycin, trimethoprim-sulfamethoxazole, and chloramphenicol. A similar outbreak occurred in Memphis, TN (7).

These experiences suggest strongly that antibiotic-resistant pneumococci are likely to become much more common over the next few years. This Grand Rounds will address the phenomenon of antimicrobial resistance in *S. pneumoniae* as it impacts on clinical management and prevention.

## Definitions: Penicillin Susceptibility and Resistance

Until recently, most clinical laboratories screened isolates of *S. pneumoniae* for susceptibility to penicillin using a 1 $\mu$g oxacillin disc. *Sensitive* isolates showed a zone of inhibition of 20 mm or greater. *Resistant* isolates showed less inhibition, 19 mm or less. When compared with minimal inhibitory concentrations, tested in broth, these criteria were less than perfect.

**Comparison of MICs and Oxacillin Screening Test Results for Selected Strains of *S. pneumoniae* (from Thornsberry (8))**

| | Oxacillin Screening Test | |
|---|---|---|
| **MIC** | **Susceptible** (≥ 20 mm) | **Resistant** (≤ 19 mm) |
| **Susceptible** (≤ 0.06 μg/ml) | 61 | 115 |
| **Intermediate** | 2 | 156 |
| **Resistant** (≥ 2 μg/ml) | 0 | 36 |

Note that many isolates that were deemed resistant by oxacillin disc were susceptible by MIC. On the other hand, isolates that were susceptible by oxacillin disc were uncommonly resistant by MIC (2/63 or 3.1%).

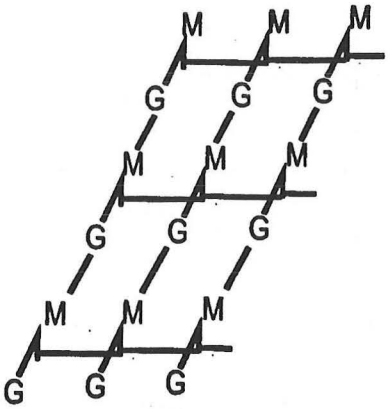
The clinical justification for the cut-off points is an attempt to approximate attainable CSF levels. ***Sensitive*** pneumococci have penicillin G MIC's equal to or less than 0.06 μg/ml. ***High level resistance*** is defined as an MIC ≥ 2 μg/ml. ***Intermediate*** or ***relative*** resistance is from 0.12 to 1.0 μg/ml. Highly resistant strains are more often resistant to non-β-lactam antimicrobials. ***Multiply resistant pneumococci*** are those with resistance to more than one commonly used antimicrobial agent.

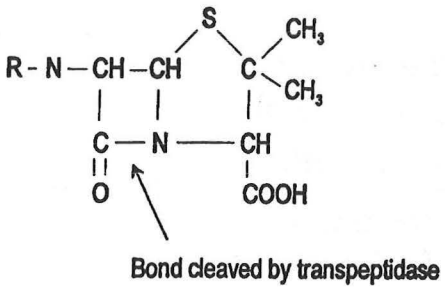
**Case report 1.** This 54 year-old diabetic woman was admitted to PMH in February, 1994, with bacterial meningitis. *S. pneumoniae* was grown from her CSF and blood. On the third hospital day, the laboratory reported that her isolate was resistant to oxacillin (inhibitory diameter = 18 mm). Her therapy was changed to include high-dose vancomycin. After she had been treated for several days, the penicillin MIC was reported by Dr. Jorgenson's laboratory in San Antonio to be 0.06 μg/ml. Vancomycin was discontinued and penicillin G was used to completeher course.

This case illustrates the major inadequacy of the oxacillin disc screening method. An improvement is the E (epsilometric) strip (9), which allows a quantitative estimate of MIC without performing broth dilution sensitivity testing. This method replaced the oxacillin disc in the PMH microbiology lab last month. It is likely that this will improve the diagnosis of penicillin resistance and reduce the unnecessary use of alternative antimicrobials.

## How Does Penicillin Kill Pneumococci?

*S. pneumoniae* is an aerobic gram-positive bacterium that usually grows in body fluids as diplococci but can form short chains. As in other gram-positive bacteria, the cell wall is composed of a net-like material called peptidoglycan or murein.

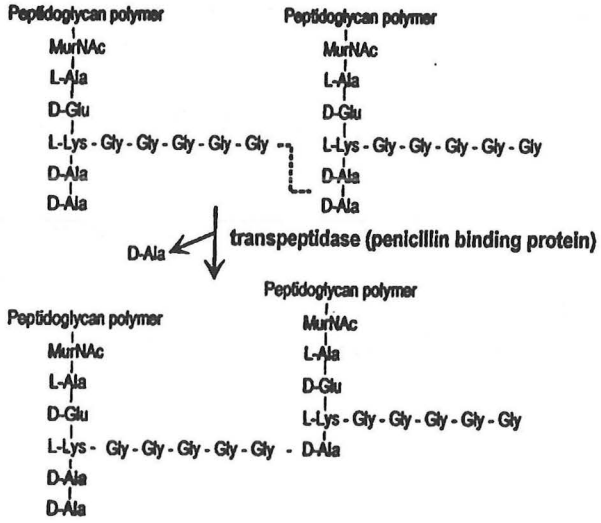



Structure of peptidoglycan (*S. aureus*). M = N-acetylmuramic acid G = N-acetylglucosamine. (Right) Structure of penicillin G.

Penicillin acts by binding to key enzymes in the peptidoglycan biosynthetic machinery. **Penicillin binding proteins (PBPs)** are active site serine enzymes. Each cell has several PBPs, some of which are known to be essential for cell viability/growth. The precise functions of all of the PBPs are not known. There is heterogeneity in the PBP composition of penicillin-sensitive pneumococcal isolates (10).

The best understood PBP is the transpeptidase that cross-links peptidoglycan polymers:

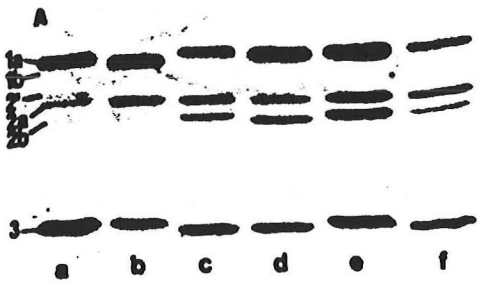


Penicillin mimics D-Ala-D-Ala. It is recognized by the transpeptidase, which cleaves the β-lactam ring. This allows the free carboxyl group to bind to the enzyme and inactivate it.

In addition to inhibiting PBPs, penicillin allows unopposed action of (or triggers) the cellular autolytic machinery--in particular, the amidase (N-acetylmuramoyl-L-alanine amidase). Recent studies have shown that there is another component to the autolytic process, the product of the cid gene, that appears to be essential for amidase activation and that allows further autolysis in amidase-deficient cells (11).

**The Molecular Basis for Penicillin Resistance in *S. pneumoniae***

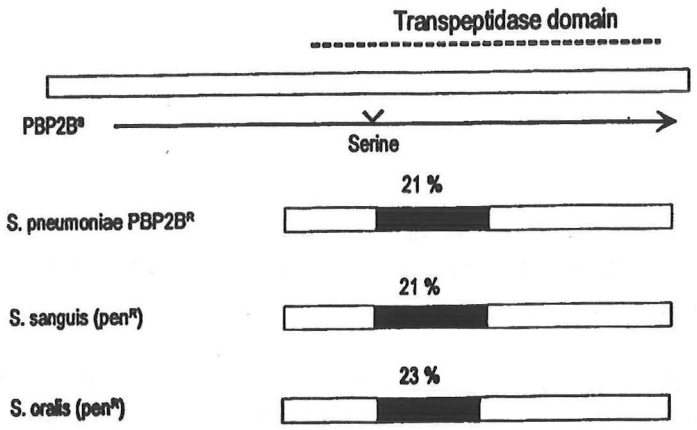
As first described by Hagenbeck et al. (12), penicillin-resistance is associated with the synthesis of high molecular weight penicillin-binding proteins (PBPs) that have reduced binding affinity for penicillin G. The degree of penicillin resistance generally correlates inversely with the level of penicillin binding observed. New PBPs can also be produced.




(Bacterial strains were incubated with [$^3$H]penicillin then lysed and analyzed by SDS-PAGE following by fluorography. Note that with increasing penicillin resistance (lanes f --> a, or from right to left in the figure) there is loss of affinity of some of the proteins for [$^3$H]penicillin. In the most resistant strain (a), there is also a new PBP (2').)

High level resistance (MIC > 1.0 μg/ml) is associated with multiple abnormal PBPs. Most often these are PBPs 2X or 2B.

Analysis of the amino acid sequences of PBPs from penicillin-sensitive and penicillin-resistant pneumococci showed that the alterations occur in discrete regions of the PBPs, as if blocks of DNA were recombined. Mosaics are often formed.




(Figure adapted from Dawson et al. (13). The PBP2B gene of a penicillin-sensitive pneumococcus is shown at the top, including the location of the transpeptidase domain and the active site serine. The sequenced regions of the PBP2B gene of a penicillin-resistant strain, and two penicillin-resistant strains of oral streptococci are shown below. The figures above the dark blocks show the percentage sequence divergence; in the regions represented by the open blocks there was < 4% divergence.)

These and other data suggest that pneumococci probably acquired penicillin resistance by genetic recombination with penicillin-resistant commensal bacteria (13,14). It is also highly likely that *S. oralis* acquired penicillin-resistance from pneumococci, and not the reverse (see below).

In at least one instance, the abnormal PBP is known to be altered in a way that should produce an abnormal penicillin binding site (15). Interestingly, peptidoglycan structure is abnormal in penicillin-resistant strains, suggesting that the altered structure of the PBPs changes their substrate preference for peptide cross-linking (16).

## Acquisition/spread of pneumococcal resistance. The "transforming principle."

### Historical review: capsular polysaccharides, transformation, DNA

(See the excellent secondary account by Musher (17) and books by two participants, Dubos (18) and McCarty (19).)

### There are distinct serotypes of *S. pneumoniae*

1891 - Klemperer and Klemperer showed that serum from rabbits injected with heat-killed pneumococci contained factor(s) that conferred immunity to reinfection with the same strain, but not to heterologous strains.

1910 - Neufeld and Handel classified patient isolates into two groups, types I and II, based on their ability to kill mice previously immunized with pneumococci referred to as types I and II.

**Serologic specificity is determined by the capsular polysaccharide**

1917 - Dochez and Avery found that the "soluble specific substance" was found in serum and urine of patients with pneumococcal pneumonia. This substance formed a precipitate with antiserum to the homologous pneumococcus. They identified the substance as polysaccharide.

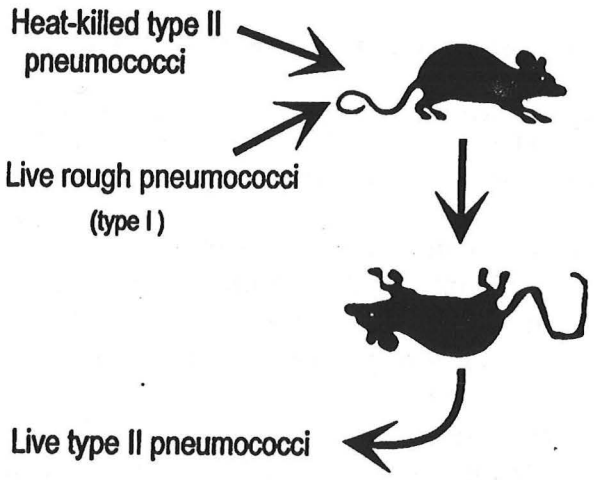
1923 - Heidelberger and Avery showed that the polysaccharide was responsible for serological reactivity. Heidelberger went on to demonstrate that the capsular polysaccharide was antigenic, and that it could induce protective immunity. (Up to this time it was generally thought that only proteins could be immunogenic.)

**Smooth and rough isolates of *S. pneumoniae* can be grown in continuous culture**

1916 - Stryker noted that when virulent strains were grown in broth containing homologous antiserum , they became less virulent and were more readily ingested by phagocytes.

Griffith defined "smooth" (S) colonies of *S. pneumoniae*, when grown on plates containing homologous immune antiserum, as possessing a mucoid phenotype attributable to the presence of the polysaccharide capsule; these organisms are virulent in animals and agglutinable in the presence of homologous antisera. Rough (R) organisms do not possess the capsular polysaccharide and are avirulent. Unlike S bacteria, they do not induce protective antibodies when injected into rabbits. Some rough forms could be propagated indefinitely, even in vivo, without reverting to the smooth phenotype.

**Rough bacteria can acquire a smooth phenotype in vivo and in vitro.**




1923 - In a seminal experiment, Griffith (20,21) injected into mice (1) heat-killed smooth pneumococci (type II) and (2) live rough pneumococci from a non-reverting strain (type I). He found that the rough form could acquire the capsular type of the heat-killed organism: only type II pneumococci were isolated from the mice.

Alloway (22) demonstrated the transformation in vitro, using extracts of *S. pneumoniae*.

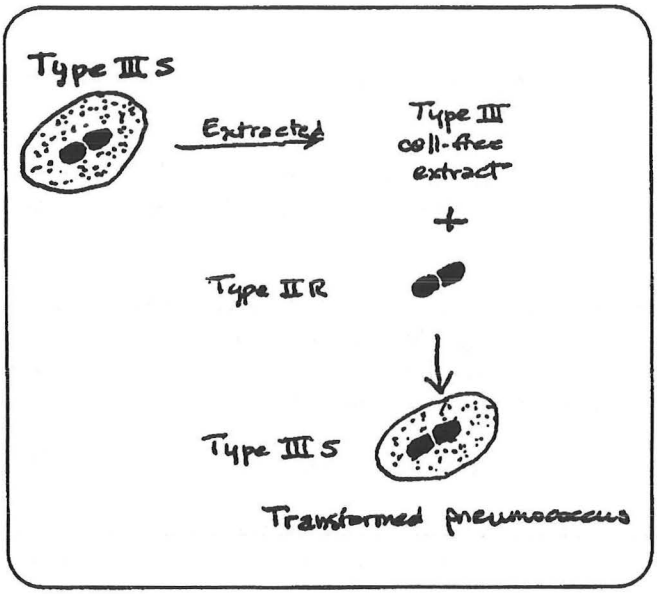



**Diagram of in vitro transformation, from McCarty (23).**

**The "transforming principle" is DNA.**

**1944 - Fifty years ago last month, a paper describing what many regard as the most important biological advance of this century was published in The Journal of Experimental Medicine (24). Oswald Avery, Colin MacLeod, and Maclyn McCarty reported that the genetic material responsible for the rough-to-smooth transformation of pneumococci is DNA.**

**Other phenotypic traits can also be transferred by DNA.**

**1951 - Hotchkiss, working in Avery's lab at the Rockefeller Institute, showed that resistance to penicillin could be transferred to a previously penicillin-sensitive pneumococcus by DNA isolated from a penicillin-resistant pneumococcus (25).**

As stated above, there is strong evidence that alterations in pneumococcal PBPs were acquired by DNA transformation from other microorganisms. Pneumococci are naturally competent for transformation (26), and acquisition of resistance in vitro can occur as single (27) or multiple steps.

As mentioned above, there is also evidence that viridans streptococci can acquire penicillin resistance from pneumococci (28). The PBP2B genes of *S. pneumoniae* and *S. oralis* are typically around 20% divergent. When a penicillin-resistant *S. oralis* was compared with a type 6 *S. pneumoniae*, the *S. oralis* PBP gene was 99% identical to the pneumocccal gene (29). It thus seems likely that DNA was transferred from *S. pneumoniae* to *S. oralis*. The potential implications of this transfer from resistant pneumococci to oral streptococci (and other bacteria) are obviously enormous.

## Geographical spread of penicillin-resistance

Analysis of multiple marker proteins has revealed that high level penicillin-resistant *S. pneumoniae* are often clonal (25,28). Apparently identical isolates of penicillin-resistant serotype 23F have been recovered in Spain and the U.S. (25). Identical, abnormal PBP genes have been found in serotype 9 isolates that are otherwise distinct from the 23F isolates, suggesting that genes encoding altered forms of PBPs have been transferred to distinct evolutionary lineages of *S. pneumoniae* (29). Interestingly, three abnormal genes (PBP1A, -2B, and -2X) appear to have been transferred simultaneously, indicating that high level resistance need not be acquired by the stepwise acquisition of abnormal PBPs.

Clonality may be detected most easily when isolates are collected from patients from a single site over a short period of time, or when the prevalence of resistant isolates in a locale is low (28). Multiresistant serotype 6B *S. pneumoniae* were evidently introduced into Iceland in 1988 (30). Over the next three years the frequency of penicillin-resistant isolates rose steeply, from 2.3%, 2.7%, and 8.4%. In the first quarter of 1992, 17% of all pneumococcal isolates were resistant. Fifty-seven of the resistant isolates were analyzed; all were found to be serotype 6B, with identical phenotypic markers. The same isolates had previously been identified in Spain, where affluent Icelanders frequently go for winter vacations.

Although it has been possible to demonstrate clonality among pneumococcal isolates and to document interesting patterns of intercontinental spread, overall it appears that penicillin-resistant pneumococci have arisen independently in many different locales (28). Studies have often found that penicillin-resistant isolates are more commonly found in individuals who have received prior antimicrobial therapy, yet spread of these strains to untreated persons has also been the rule. Antibiotic pressure is not necessary for the strains to spread within a community.

## Pneumococcal resistance to other antimicrobials

**Other β-lactams.** Resistance to penicillin G correlates strongly with resistance to other penicillins (ampicillin, ticarcillin, etc.). Since resistance is not mediated by β-lactamases, the isolates are also resistant to combinations such as ampicillin/clavulanate. **Cephalosporin resistance** is also associated with altered PBPs (31). Both incremental (two-step) and single-step acquisition of resistance have been demonstrated in vitro. Cephalosporin and penicillin resistance may involve different PBPs, so that cephalosporin-resistant isolates may not be highly resistant to penicillin, and vice versa.

In vitro susceptibility of penicillin-susceptible and -resistant *S. pneumoniae* to other antimicrobials.
From I. R. Friedland and G. H. McCracken,Jr.

| ANTIMICROBIAL | PCN-sensitive | Relative resistance | High level resistance |
|---|---|---|---|
| Cephalexin | 100* | no data | no data |
| Cefaclor | 100 | 67 | 7 |
| Cefuroxime | 100 | 50-90 | < 50 |
| Cefotaxime | 100 | 100 | > 90 |
| Ceftazidime | 90 - 100 | < 50 | 0 |
| Imipenem | 100 | 100 | 90 - 100 |
| Chloramphenicol | 96 - 99 | 90 - 100 | 100 |
| Erythromycin | 94 - 99 | 69 - 100 | 21 |
| Trimethoprim/sulfa | 94 - 100 | 58 - 100 | 73 |
| Vancomycin | 100 | 100 | 100 |

* Percent of strains susceptible in vitro

These data were compiled from several reports in the literature (34).

Note that some extended spectrum cephalosporins (cefotaxime, cefuroxime, ceftriaxone) are more effective than others (ceftazidime, cefixime). Of the oral cephalosporins, penicillin-resistant *S. pneumoniae* from the U.S. are most sensitive in vitro to cefprozil and cefuroxime axetil, less sensitive to cefaclor and loracarbef, and least sensitive to cefixime (8,35).

New criteria for interpreting the results of in vitro antimicrobial susceptibility tests for drugs other than penicillin have recently been proposed (36).

**Non-β-lactam antimicrobials.** Note that penicillin-resistant isolates are often resistant to commonly used drugs such as trimethoprim-sulfamethoxazole, tetracycline, and erythromycin. The molecular mechanism for acquisition of these resistance genes is uncertain. Isolates that are resistant to erythromycin are usually resistant to newer macrolides such as clarithromycin.

The susceptibility of pneumococci to quinolones is unrelated to their susceptibility to penicillins. However, ciprofloxacin, ofloxacin, and norfloxacin are only marginally effective toward pneumococci and should not be used. Newer quinolones such as clinafloxacin and sparfloxacin are much more effective vs. pneumococci in vitro (37,38) and may have clinical promise.

Penicillin-resistant isolates remain uniformly susceptible to vancomycin (MIC $\leq$ 4 $\mu$g/ml) and are also usually susceptible to rifampin. There are few published data regarding susceptibility to clindamycin.

**Summary:**

1. Penicillin resistance is caused by genetic alterations in the genes that code for the enzymes (PBPs) that are normally inactivated by penicillin. The abnormal PBPs bind penicillin with greatly reduced affinity.

2. Penicillin resistance has arisen in many different places and can be associated with mutations in many different PBPs. In most instances, it has been possible to conclude that blocks of DNA were acquired by recombination with DNA from other bacteria. Pneumococci may become resistant in an incremental fashion, acquiring sequential abnormalities in several PBPs, or they may acquire mutations in several PBP genes in a single transformation step.

3. Some penicillin-resistance genes have behaved in a clonal fashion, with spread to many distant locales and transfer to other serotypes of *S. pneumoniae*.

4. Strains that are highly resistant to penicillin are often also resistant to multiple other antimicrobials.

5. Penicillin resistance is a stable trait that does not require antimicrobial pressure to persist and spread within a population.

6. Since most other streptococci are competent for transformation, the potential for widespread acquisition of penicillin resistance by these bacteria is great.

**THERAPY**

Most diseases caused by relatively resistant *S. pneumoniae* can be treated with high intravenous doses of penicillin G or other β-lactams (39). A number of other drugs are also usually effective, including many cephalosporins. Since very high concentrations of these drugs are achieved in the blood, lung, and other tissues, it has generally been possible to achieve therapeutic success with moderately resistant organisms. Treatment failures have been reported with

highly resistant pneumococci, however, and alternative agents have been used--most frequently, vancomycin. At the moment, the frequency of highly resistant pneumococci in Dallas is not sufficiently great to recommend a change in the empiric therapy of community-acquired pneumonia, bacteremia, or otitis media (32).

For effective therapy of meningitis, however, concentrations of the antimicrobial drug must exceed the MIC of the pneumococcus by 8-fold or greater. High-dose penicillin has been ineffective. Pediatric infectious disease experts recommend treatment with an extended spectrum cephalosporin (cefotaxime or ceftriaxone) (32), although failures have been reported with these agents (38) and alternative regimens are being evaluated. One approach is to substitute vancomycin (meningeal dose: 50 mg/kg/day in patients with normal renal function) for β-lactam therapy until the susceptibility of the isolate to penicillin (or cephalosporin) is known. Another is to use both a cephalosporin and vancomycin; in an animal model, this combination was synergistic even for a cephalosporin-resistant isolate (39). A third approach is to add rifampin (300 mg q8h) to the cephalosporin regimen. Imipenem-cilastatin should be avoided because it is associated with a high incidence of seizures in patients with meningitis (32). In any case, the regimen should be adjusted when the results of susceptibility testing are available. If the isolate is susceptible to penicillin, use it! Infectious Disease consultation is advisable in most instances.

Note that vancomycin has not been uniformly efficacious for the treatment of pneumococcal meningitis (40), even when high doses were used. It is important to repeat the CSF gram-stain and culture 48 hours after initiating therapy, since treatment failures may be detected in this way. Dexamethasone may decrease the penetration of vancomycin into the CSF (M. Paris, S. M Hickey, M. I. Uscher, et al., manuscript submitted for publication). Rifampin may act synergistically with vancomycin, although careful studies in adults with meningitis have not been reported.

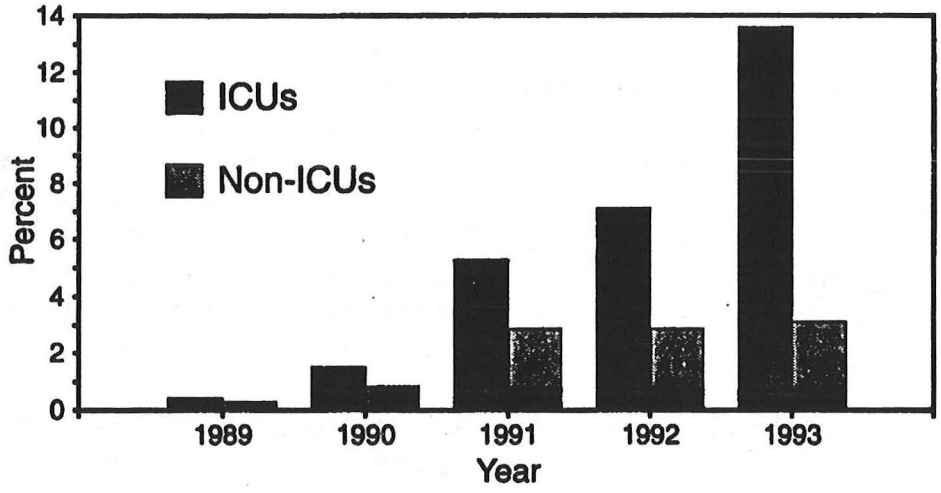
**Case report 2.** This 28 year-old HIV-infected man presented to the Parkland Memorial Hospital emergency room after 4 days of cough and fever. The chest X-ray showed an infiltrate in the right upper lobe. He was treated with ticarcillin/clavulanic acid (3.1 gm q4h) and gentamicin. Blood cultures were positive for *S. pneumoniae*. The CD4 count was 60/mm$^3$. Six days after admission he was noted to be lethargic. The CSF had 19,000 nucleated cells/mm$^3$; the glucose concentration was 10 mg/dl. Gram-stain of the CSF showed numerous gram-positive diplococci and grew *S. pneumoniae*. His therapy was changed to vancomycin and he improved.

Neither of the pneumococcal isolates was inhibited by a 1 μg oxacillin disc. Penicillin MICs for the 2 isolates were 0.25 and 0.5 μg/ml, respectively.

This case indicates that pneumococcal meningitis can develop even during apparently effective therapy for relatively resistant pneumococcal pneumonia with bacteremia. It seems likely that the meninges were seeded at the time of admission and that the ticarcillin simply delayed the onset of clinical meningitis. In the absence of inflammation, most ß-lactams do not penetrate into the CSF very well. Many of the reported cases of treatment failure using high-dose penicillin have been in immunocompromised hosts.

**Vancomycin resistance in enterococci**

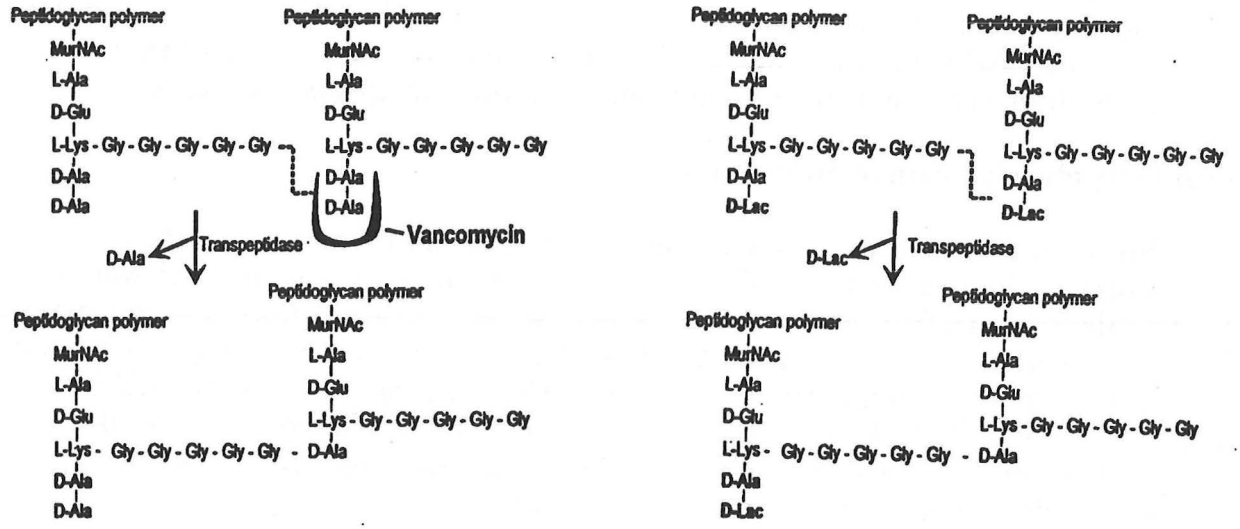
Since vancomycin is the only effective drug for many highly resistant pneumococci, the development of vancomycin resistance in pneumococci would be a major calamity. In fact, such resistance is now recognized in *Enterococcus* species. A CDC surveillance program reported that the percentage of vancomycin-resistant enterococci isolated from patients in ICUs in the U.S. increased from 0.4% in 1989 to 13.6% in 1992 (41). Frequently the strains are also highly resistant to β-lactams and aminoglycosides. Isolation of these strains from the blood is associated with substantially increased mortality.




**(Percentage of nosocomial enterocci reported as resistant to vancomycin isolated from infections in patients in ICUs and non-ICUs, by year -- National Nosocomial Infections Surveillance system (41). Data for 1993 are through March.)**

Patients who develop infection with these strains have usually been hospitalized for prolonged periods, have received vancomycin, and/or have received prolonged courses of other antibiotics (42-45). In one outbreak (44), transmission of infection was traced to an electronic rectal thermometer. A popular speculation is that resistant enterococci can be selected by using enteral vancomycin for treatment of antibiotic-induced colitis. Isolation of vancomycin-resistant enterococci has been associated with large hospital size and affiliation with a teaching institution (41).

**Vancomycin: mechanism of action.** Vancomycin is a complex glycopeptide that binds to D-Ala - D-Ala at the terminus of the pentapeptide, thereby interfering with transpeptidation (48,49).




(Left) Vancomycin mechanism of action (Right) Mechanism for vancomycin resistance.

**Molecular basis for resistance.** Resistance to vancomycin requires at least 2 or 3 genes (49). VanH is a dehydrogenase that produces D-lactate from pyruvate. VanA is a ligase that joins D-Ala and D-lactate to produce the depsipeptide D-Ala-D-Lac. This depsipeptide then is substituted to the end of the pentapeptide instead of D-Ala-D-Ala. Therefore the pentapeptide ends in D-lactate. Vancomycin does not bind to D-Ala-D-Lac, so it can have no effect on cell wall synthesis. There are also other mechanisms for vancomycin resistance (50). Van B produces lower-level vancomycin resistance, for example.

Synthesis of the enzymes that produce vancomycin resistance is inducible by vancomycin (51). Resistance may not be apparent when routine susceptibility testing is done.

Vancomycin resistance genes are located on a transposon that has the ability to transfer genes to many other bacteria (49,52), probably including pneumococci.

**Recommendations.** Vancomycin should be used much more cautiously than is currently the practice. Some examples:

a) Given the existence of vancomycin resistance in enterococci, the possibility that enteral vancomycin may select such resistant strains, and the potential for vancomycin resistance to spread to other common bacteria, oral vancomycin should not be used routinely for prophylaxis (bowel decontamination) or for the

initial therapy of antibiotic-induced colitis in patients with mild disease. Patients who receive oral vancomycin should be isolated.

b) Empiric use of vancomycin in febrile, neutropenic patients should also be limited, since good studies indicate that it is not necessary and may be toxic, even in patients with indwelling catheters (53,54). Unfortunately, exceptions are often necessary in hospitals in which methicillin-resistant *S. aureus* are prevalent (e.g., Parkland and Zale-Lipshy); in such locations, empiric vancomycin should be used in febrile, neutropenic patients with indwelling intravenous catheters.

c) Many patients are treated with vancomycin for methicillin-sensitive *S. aureus* diseases when other agents (e.g., nafcillin) would suffice.

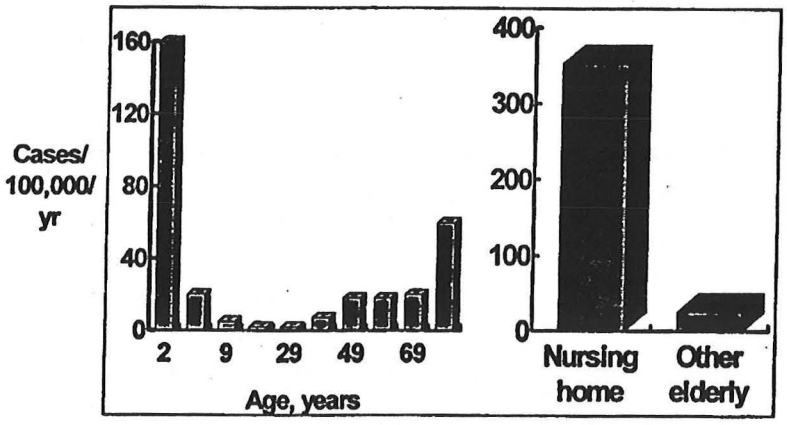
Many outbreaks of vancomycin-resistant enterococcal infection in ICUs have been controlled by patient isolation and other routine hospital infection control practices. These practices, used routinely, also should help prevent the spread of resistant isolates.

## PREVENTION

### Epidemiology of pneumococcal infection

*S. pneumoniae* spreads via respiratory droplets from person to person. Many individuals in a population are colonized with *S. pneumoniae* at any given time. Most children are colonized with pneumococci at some point during the first two years of life (55).

Attack rates for invasive (bacteremic) pneumococcal disease have recently been studied in Oklahoma City (5). Rates were highest in infants and children less than 4 years of age (70/100000/yr) and persons 60 years of age or older (42.1/100000/yr). These rates are somewhat lower than reported in studies from other areas in the U.S. (56,57). The incidence of pneumococcal pneumonia can be several (3 - 5) times greater than the detected rate of invasive disease.




Rates of pneumococcal disease in the population of Charleston,S.C., by age (57) (left) and a comparison of rates in nursing home residents and other elderly Oklahomans (5) (right).

In families, asymptomatic pneumococcal carriage is related to age:

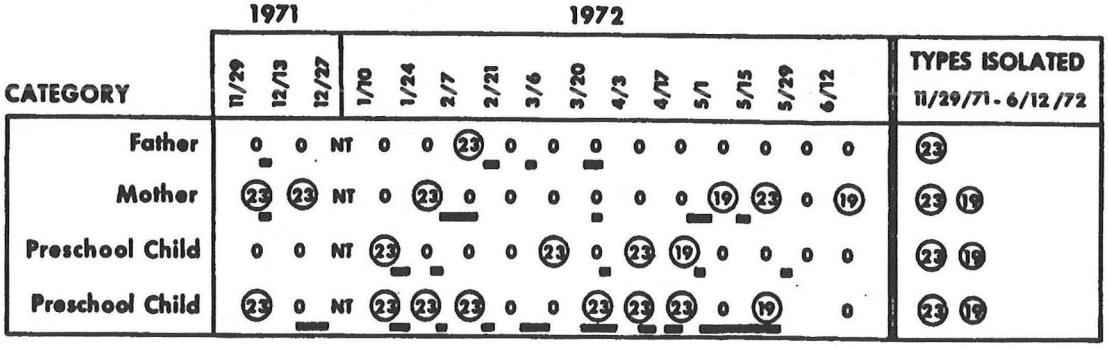
Detection of *S. pneumoniae* in nose and throat samples (from reference (56).

| Group (age in years) | No. in group | Carriage (No. positive/total tests (% positive) |
|---|---|---|
| Preschool children <5 | 18 | 123/325 (38) |
| Grammar school children (6 - 12) | 13 | 76/261 (29) |
| High school students (13 - 17) | 5 | 12/138 ( 9) |
| Adults (≥ 18) | 29 | 111/581 (19) |
| Total | 65 | 322/1,305 (25) |

In this careful longitudinal study of families in Charlottesville, VA, in the 1970's, the median duration of carriage of a serotype of *S. pneumoniae* was two weeks in children and four weeks in adults. In adults, rates of carriage correlated inversely with the age of the children in the home (higher rates of carriage when there were younger children).

Other studies have also found higher rates of carriage of penicillin-resistant pneumococci in young children than in older children or adults (3), in keeping with the pattern described above.

A typical pattern of spread of pneumococci within a family is illustrated in the following figure from reference (57).



(See Figure on previous page. The numbered serotype isolated from each individual on each date is circled. The occurrence of upper respiratory symptoms is indicated by a dark bar. Note (1) carriage is intermittent, even in the same individual (this may represent sampling error); (2) a new isolate (serotype 19) was introduced on 4/17 by a preschool child, who then spread it to the mother and a sibling; and (3) there was little relationship between carriage and upper respiratory symptoms. In the total population studied, carriers were more likely to transmit pneumococci to another family member when they had respiratory symptoms. In one instance, simultaneous spread of *S. pneumoniae* and a rhinovirus was documented.)

In earlier studies, workers found that crowding was a strong risk factor for intrafamilial spread of *S. pneumoniae*.

Much less is known about the spread of pneumococcci among the adults in communities. Children do not constitute the only reservoir of infection, since the serotypes that cause disease in adults in a community are often different from those that cause disease in children. On the other hand, although the CDC refused to release the relevant data for this presentation, it appears that the same few pneumococcal serotypes have been associated with penicillin-resistance in both adults and children in the U.S., suggesting that for these strains the pediatric reservoir may be very important for spread within the entire population.

**Outbreaks of pneumococcal disease.** Outbreaks of pneumococcal disease have usually occurred in populations who live in confined, crowded conditions--such as prisoners, homeless men in shelters (60), military recruits, South African miners (who live in crowded barracks), elderly individuals living in nursing homes (61), hospital wards (2,62), and children in day-care centers (63). In Oklahoma City in 1989, the attack rate for residents of nursing homes (352/100000) was 13 times higher than the attack rate for elderly patients who did not live in nursing homes (25.6/100000)(5). The rates of pneumococcal bacteremia in certain Native American populations may be several-fold higher than the rate in the general population.

**Outbreak report:** In September, 1989, 12 cases of invasive pneumococcal disease occurred in inmates at a Harris County jail (64). Two patients died. All isolates were serotype 12. Many of the patients had underlying conditions including alcoholism, IV drug abuse, cirrhosis, and asplenia. All cases were male; their ages ranged from 19 to 53 years.

The jail was constructed to hold 3500 inmates but at the time of the outbreak it housed a daily average of 6900 inmates. Cases occurred on 7 of the 10 floors used to house inmates. No cases occurred in 950 staff members.

**Summary: epidemiology of pneumococcal infection and disease**

1. Pneumococci are transmitted person-to-person by respiratory droplet spread.

2. Most strains are introduced into families by children, who evidently acquire infection at day care centers or other sites in the community. Infection spreads to other children and to adults, with intermittent/persistent carriage for weeks to months.

3. Many different serotypes cause disease in children and adults. There is limited overlap between age groups, although some of the more common pediatric serotypes (such as 6 and 14) are also common among adults.

4. Outbreaks have usually occurred in physically contained, crowded groups--barracks, day care centers, nursing homes, prisons, etc.

**Risk factors for infection with penicillin-resistant pneumococci.**

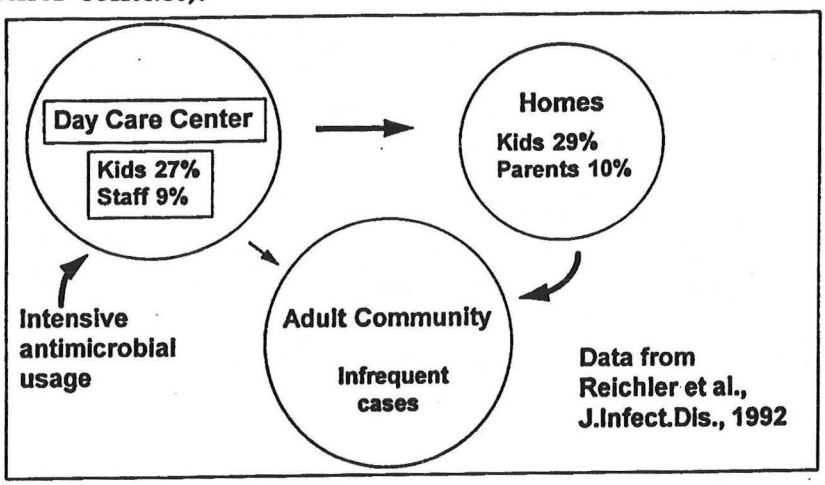
Of the risk factors identified for the acquisition of resistant pneumococci in hospitalized patients, antimicrobial therapy is probably the most important. In a longitudinal study carried out in Baragwanath Hospital, Johannesburg, in 1988, children who received β-lactam therapy were much more likely to be discharged carrying resistant pneumococci (87% of carriers) than those who did not receive β-lactam (59%), and the isolates were more likely to be highly resistant (3).

In contrast, other South African studies showed that children who received benzathine peniciilin therapy for the prevention of rheumatic fever did not have increased carriage rates for resistant pneumococci (3), nor did their family members.

A more recent study of a day-care outbreak in Ohio found that using prophylactic antibiotics was a risk factor for nasopharyngeal carriage of resistant pneumococci (63). *S. pneumoniae*, serotype 23F, resistant to multiple antimicrobials, was isolated from the middle ear fluid of a child with otitis media who attended a day care center in Cleveland, Ohio (63). Investigation of the day care center found that 27% of the 250 children and 2 of 26 staff members were nasopharyngeal carriers of the resistant strain, as were 14% of the family members of children carrying the strain (29% of the children and 10% of the adult family members). Carriage was more common in infants and younger children. No resistant isolates were obtained from 121 children at two nearby day care centers.

The strain was also isolated from 2 children who left the center 13 months prior to the investigation, from the sputum of a woman with bronchitis who lived

in the community where the day care center was located (no other contact), and from the sputum of a man with pneumonia who lived in another suburb of Cleveland (no other contact).




(Prevalence of nasopharyngeal carriage of serotype 23F penicillin-resistant *S. pneumoniae* in residents of Cleveland, Ohio, 1989)

The day care center was an incubator for penicillin-resistant pneumococci in this community. The "heat" was antibiotic use--children who had taken 3 or more courses of antibiotics during the previous 3 months were 7.3-fold more likely to carry the resistant strain. Transmission occurred to the families of these children, and, much more infrequently, cases of disease caused by the same strain were noted in the adult community (the carriage rate in community adults was not studied).

## Risk factors for disease caused by penicillin-resistant pneumococci

When compared with patients who develop invasive pneumococcal disease caused by penicillin-sensitive strains, adult patients with penicillin-resistant pneumococcal disease often have identifiable characteristics: more frequent use of β-lactam antibiotics during the previous 3 months, nosocomial acquisition of disease, and a serious underlying disease (39). Not all cases have such risk factors, however (62).

A recent patient is illustrative:

**Case Report 2.** This 77 year-old man with known non-Hodgkins lymphoma (since 1975) and prostate cancer (since February, 1993) was admitted to Zale-Lipshy Hospital in August, 1993, for evaluation of cough and fever that had not responded to one month course of oral amoxicillin/clavulanate. A computed tomographic examination showed hilar lymphadenopathy and a lower-lobe pulmonary infiltrate. He was treated with intravenous cefuroxime and improved. He was readmitted on November 18, 1993, with recurrent pneumonia; blood cultures grew *S. pneumoniae*. He again improved with cefuroxime and he

was discharged to take oral cefuroxime-axetil. Two days after stopping the oral antibiotic he was readmitted with recurrent fever and his blood cultures again grew *S. pneumoniae*. He was treated with intravenous vancomycin and improved.

Neither of his isolates was inhibited by a 1 μg oxacillin disc. The MICs of the second isolate, determined in Dr. Jorgenson's laboratory in San Antonio, were (in μg/ml): penicillin G, 0.25 (relatively resistant); cefuroxime, ≤ 0.5 (sensitive), erythromycin, ≤ 0.06, vancomycin, 0.5, and trimethoprim-sulfamethoxazole, 0.25/4.75.

This man's pneumococcal strain was relatively resistant to penicillin G yet it was sensitive to all of the other antimicrobials tested. It is hard to attribute his clinical failure simply to drug resistance; underlying disease (lymphoma) with impaired antibody formation and perhaps poor lymphatic drainage of the involved lung may have contributed. The cefuroxime treatment only suppressed his infection, however.

## Pneumococcal virulence

*S. pneumoniae* is a classical encapsulated pathogen and much of its virulence, immunology, and serology is related to the capsular polysaccharide. There are 83 capsular types. Neutralizing antibodies to the capsular polysaccharide are protective in animal infection models.

Of the 80+ serotypes, certain ones are most commonly isolated from the blood or CSF. Recently in the U.S., these have included types 3, 4, 14, and 19 (55). Most epidemics of pneumococcal disease (penicillin-sensitive strains) have been associated with serotypes 1, 2, 3, 5, 8, and 12F (55). The molecular mechanisms underlying these observations are not known.

In addition to the capsular polysaccharide there is the cell wall ("C") polysaccharide, with which C-reactive protein reacts. Much of the host response to pneumococci appears to be elicited by the cell wall itself--the murein or peptidoglycan. Discrete fragments of peptidoglycan have different inflammatory potency, and, at least in the cerebrospinal fluid of rabbits, some of these fragments are as potent as gram-negative bacterial endotoxin.

Although controlled studies are not possible, it appears that, at least in South African children, penicillin-sensitive and penicillin-resistant pneumococci cause a similar spectrum of illness (65). There is little evidence that penicillin resistance is associated with greater virulence.

## Immunity

Humoral immunity is paramount. IgG antibody to the capsular polysaccharide is protective. In the absence of specific anti-capsular antibody,

antibody to cell wall antigens attaches to the bacterial surface, where it binds complement. The surrounding capsule prevents both IgG (Fc) and complement from engaging receptors on phagocytes, so that phagocytosis does not occur. Specific anticapsular antibody, in contrast, binds to the surface of the capsule, opsonizing the bacterium for phagocytosis by Fc- and/or iC3b-mediated mechanisms.

For many years, measurements of antibodies to pneumococcal capsular polysaccharides were performed using a RIA. Musher and colleagues have recently reported that this assay does not cleanly distinguish antibodies to capsule from antibodies to cell wall polysaccharides (24). They developed a more specific ELISA test and found that most healthy young adults lack antibody to most capsular polysaccharides (24). Antibody to cell wall polysaccharide is not protective in an animal model and probably not in humans (25).

Recent outbreaks in military personnel allowed workers to study the relationship between colonization and the appearance of anti-capsular antibody. Although most recruits did not have preexisting antibody to the colonizing serotype, anti-capsular IgG appeared within a week or two of documented colonization (Musher, data not provided). This is similar to the time course of the appearance of antibody following polysaccharide vaccine (66). Musher thinks that most cases of pneumococcal disease occur within a short time after colonization; those who develop antibody are protected, while those who have impaired pulmonary clearance mechanisms or do not make antibody are likely to develop disease.

Antibody responses to pneumococcal polysaccharides are genetically controlled. An interesting study in Danish twins (67) found a significantly closer correlation in mean IgG2 antibody concentrations after vaccination in monozygotic than in dizygotic twins. This correlation was greater for some pneumococcal types than others.

Patients with defects in immunoglobulin production, such as those with multiple myeloma, lymphoma, chronic lymphocytic leukemia, etc., have an increased risk of invasive pneumococcal disease. Patients with sickle cell disease are also at risk for severe pneumococcal disease. A group in France recently reported that patients with sickle cell disease who acquire infection with HIV are at extraordinarily high risk of acquiring severe pneumococcal disease (4 cases in 8 adult sicklers with HIV vs. 1 case in 275 non-HIV-infected patients with sickle cell disease). None of the HIV-infected individuals had AIDS; the follow-up period was 4.6 years. The cases of disease were all severe: septic shock or meningitis.

**Pneumococcal vaccine**

As currently formulated, pneumococcal vaccine contains 23 capsular polysaccharides. Originally shown to prevent bacteremic pneumococcal disease in immunocompetent South African miners and American children with sickle cell disease (in a nonrandomized trial), the efficacy of the vaccine for other patient groups has been controversial (68). All studies in populations of elderly and/or chronically ill patients have been done post-licensure, using case-control and other indirect methodologies for estimating vaccine efficacy. Although these studies have reached different conclusions, government experts feel that the existing data support the use of pneumococcal vaccine in selected populations (56). Others feel strongly that the vaccine has not been shown to be efficacious in high risk populations and discourage its use (68).

The only published, prospective study of pneumococcal vaccine in adults at high risk of pneumococcal disease was carried out in 1981-1985 by the Veterans Administration (69). They enrolled 2295 high-risk patients in a randomized, double-blind, placebo-controlled trial of the 14-valent vaccine. High-risk patients were those who were above 55 years of age and had chronic cardiac, pulmonary, renal, or hepatic disease, alcoholism, or diabetes mellitus; patients with immunocompromising diseases such as multiple myeloma were excluded. In this trial, vaccination did not prevent pneumococcal pneumonia or bronchitis (there were too few bacteremic episodes to study invasive disease), and the immune responses of the vaccinees who developed disease were poor.
The experts who favor pneumococcal vaccination argue that the diagnosis of non-bacteremic pneumococcal infections is relatively imprecise, and that these diseases are also associated with lower morbidity than bacteremic pneumococcal disease.

The experience with vaccination to prevent bacteremic (invasive) disease in adults is also inconsistent, however. The Table summarizes the results of several trials.

The recent study by Shapiro et al. (70) is particularly useful. It was a case-control study performed in 11 large hospitals from 1984-1990. 1054 patients with invasive pneumococcal disease were compared with an equal number of matched controls. Vaccine efficacy was 56% overall; for a subgroup of 808 immunocompetent patients the vaccine efficacy was 61%, and for a subgroup of 175 immunocompromised patients it was 21% (not different from control). The vaccine was not effective against pneumococcal serotypes not contained in the vaccine. Vaccine efficacy was also related to age and the length of time since vaccination:

Efficacy of pneumococcal vaccination in U.S. populations:
prevention of bacteremic disease. Post-licensure analyses of efficacy.

| Location | Author | Method | No. persons | Type of infection | Vaccine efficacy | 95% C.I. |
|---|---|---|---|---|---|---|
| Conn. | Shapiro | Case-control | 543 cases<br>543 controls | VT, VT-related | 61 | 42, 73 |
| Philadelphia | Sims | Case-control | 122 cases<br>244 controls | All types | 70 | 37, 86 |
| Denver | Forrester | Case-control | 89 cases<br>89 controls | All types | -21 | -221, 55 |
| CDC-1 | Bolan | Epidemiologic | 249 vaccinated<br>1638 unvaccinated | VT | 64 | 47, 76 |
| CDC-2 | unpublished | Epidemiologic | 240 vaccinated<br>1527 unvaccinated | VT | 60 | 45, 70 |
| Conn. (70) | Shapiro | Case-control | 1054 cases<br>1054 controls | VT | 56 | 42, 67 |

Adapted from Table 1 in reference (56). VT = vaccine serotype

| Age (YR) | No. of case-control pairs | Time since vaccination | | |
|---|---|---|---|---|
| | | < 3 yr | 3 - 5 yr | > 5 yr |
| | | percent protective efficacy | | |
| <55 | 125 | 93 | 89 | 85 |
| 55-64 | 149 | 88 | 82 | 75 |
| 65-74 | 213 | 80 | 71 | 58 |
| 75-84 | 188 | 67 | 53 | 32 |
| ≥ 85 | 133 | 46 | 22 | -13 |

**From E.D. Shapiro et al., New Eng. J. Med. 325:1453, 1991**

So three factors decreased the vaccine's efficacy:

*immunocompromise, age, and time since vaccination.*

Overall it appears that the 23-valent pneumococcal vaccine has approximately 50 - 70% efficacy in immunocompetent adults, including individuals over 65 years of age, when invasive disease is studied. Its efficacy is substantially lower in immunocompromised individuals (particularly those with defects in immunoglobulin production or half-life, such as multiple myeloma, lymphoma (71), or nephrotic syndrome). Several studies found that it was also less effective in alcoholics, although this subgroup has not been studied prospectively.

Note also that the vaccine serotypes account for only 80 - 90% of the isolates associated with bacteremic disease in adults. Applying this figure to the Shapiro et al. estimates, vaccination could be expected to reduce pneumococcal invasive disease by approximately 50% in immunocompetent elderly adults but only by 18% in the immunocompromised (if the vaccine efficacy in the latter group is actually different from control). Even if the vaccine were able to prevent non-invasive disease (which the VA study suggests it doesn't), only 70% of the isolates from patients with pneumonia and bronchitis may be vaccine serotypes (69).

Revaccination (booster) with pneumococcal vaccine, if carried out a year or more after the primary vaccination, is evidently not associated with an increased frequency of local side effects, as once feared, but the increase in antibody titer following booster immunization is only to ± 40% of the original post-vaccination levels (66). There is no evidence that persons who do not respond to the first vaccination will do so following the second (68).

Cost-effectiveness considerations are also controversial. If the incidence of invasive pneumococcal disease in the elderly is around 50 cases/100,000 population, and vaccination could prevent 50% of these cases, 25 cases could be avoided for each 100,000 patients vaccinated. At $20 per inoculation, this would cost approximately $80,000 per case prevented.

## Current vaccination recommendations from the CDC (56):

**Adults**

1. Immunocompetent adults who are at increased risk of pneumococcal disease or its complications because of chronic illnesses (e.g., cardiovascular disease, pulmonary disease, diabetes mellitus, alcoholism, cirrhosis, or CSF leaks) or who are $\geq$ 65 years old.
2. Immunocompromised adults at increased risk of pneumococcal disease or its complications (e.g., persons with splenic dysfunction or anatomic asplenia, Hodgkin's disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, or conditions such as organ transplantation associated with immunosuppression).
3. Adults with asymptomatic or symptomatic HIV infection.

**Children**

1. Children $\geq$ 2 years old with chronic illnesses associated with increased risk of pneumococcal disease or its complications (e.g., anatomic or functional asplenia [including sickle cell disease], nephrotic syndrome, CSF leaks, and conditions associated with immunosuppression.
2. Children $\geq$ 2 years old with asymptomatic or symptomatic HIV infection.
3. The currently available 23-valent vaccine is **not** indicated for patients having recurrent upper respiratory tract disease, including otitis media and sinusitis.

**Special groups**

Persons living in special environments or social settings with an identified increased risk of pneumococcal disease or its complications.

**Timing of vaccination**

When elective splenectomy is being considered, pneumococcal vaccine should be given at least 2 weeks before the operation, if possible. Vaccination should also ideally precede organ transplantation or cancer chemotherapy (or other immunosuppressing therapies) by at least 2 weeks.

## Pneumococcal disease and vaccine efficacy in HIV-infected individuals

Patients with HIV infection are at greatly increased (approximately 100-fold) risk for pneumococcal disease (72,73), reflecting an underlying defect in B-cell function (74,75). More than half of the infections occur in HIV-infected persons without AIDS (73). Unusual manifestations have been reported in patients with simultaneous HIV and pneumococcal disease (purpusa fulminans, mediastinitis with chest wall abscess, multiple brain abscesses, exudative pleural effusion)(7).

HIV-infected individuals with greater than 500 CD4 cells/mm$^3$ respond normally to pneumococcal vaccine (21). Those with lower CD4 counts respond to fewer antigens and make less antibody; most of these individuals were taking AZT, which may diminish antibody responses. Among responders, regardless of CD4 count, anti-pneumococcal polysaccharide antibody titers decline over time at the same rate as in normal controls: after 1 year the proportion of responses

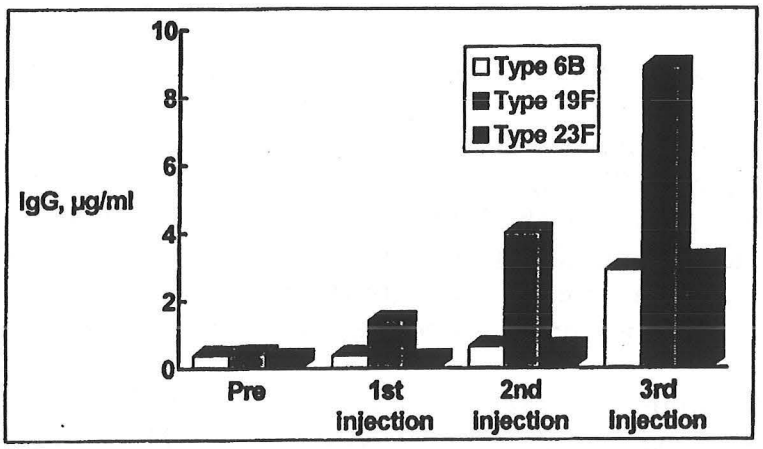
remaining over 1 μg/ml was 78% for HIV-infected patients and 74% for controls (76). *The efficacy of pneumococcal vaccine for preventing disease in HIV-infected persons is unknown.*

A cost-effectiveness analysis, using general assumptions regarding vaccine efficacy, supported the use of pneumococcal vaccination in HIV-infected persons (77). The vaccine should be given when HIV infection is first diagnosed.

## New Strategies for Improving Pneumococcal Vaccination Efficacy

**Conjugate vaccines** (78,79). Merck currently is testing a heptavalent pneumococcal conjugate vaccine (each polysaccharide is conjugated to an outer membrane protein preparation from Group B *Neisseria meningitidis*). It contains serotypes 6B, 14, 19F, 23F, 18C, 4, and 9V. It is immunogenic, with good booster responses, in adults, 2 month-old infants, and children 2 - 5 years of age (Paul M. Mendelman, M.D., Merck Research Laboratories, personal communication). An ongoing efficacy trial is evaluating its ability to prevent otitis media in infants. The anticipated completion date for this trial is mid-1995. Lederle-Praxis and Pasteur-Merieux also are producing pneumococcal conjugate vaccines.

Covalently linking polysaccharides to protein carriers allows the polysaccharide to be processed as a thymus-dependent antigen, greatly increasing its immunogenicity in young children. This strategy has worked very successfully for preventing *Haemophilus influenzae* type b disease in children (80). Producing a pneumococcal vaccine will be much more challenging, however. It is actually a combination of many different vaccines, each with its own technical difficulties (the conjugation chemistry differs for different polysaccharide structures).




(Immunogenicity of pneumococcal conjugate vaccine (3 of 7 serotypes) in 2 month-old infants (data provided by Dr. Mendelman at Merck). Note different responses to different polysaccharides, booster responses.)

A major problem is posed by serotype variability. Whereas the 7-valent vaccine would cover around 80% of the serotypes isolated from young infants, it would include only 40% of the serotypes isolated from adults with invasive disease. The 23-valent vaccine covers 80 - 90% of the isolates from adults. On the other hand, penicillin-resistance has been noted in relatively few serotypes in the U.S.:

**How many serotypes would have to go into a vaccine to prevent, say, 80% or more of *penicillin-resistant* pneumococcal disease?**

Rural Kentucky, children, 1993 (7): 6A, 6B, 19F, 23F (87% of all resistant isolates)
Memphis, Tennessee, children, 1993 (7): 6B, 19A, 19F, 23F (79%)
Oklahoma City, all ages, 1989-1990 (5): 14, 23F, 19A (91%) (high resistance: 35B, 23F)
U.S., all ages, 1979-87 (4): 14, 19F, 6A/B, 23F (81%)

So only a few serotypes have been associated with penicillin-resistant pneumococcal disease. The proposed polysaccharide-protein conjugate vaccines contain all of these serotypes except for 19A (which may cross-react with 19F, which is in the vaccines) and 35B.

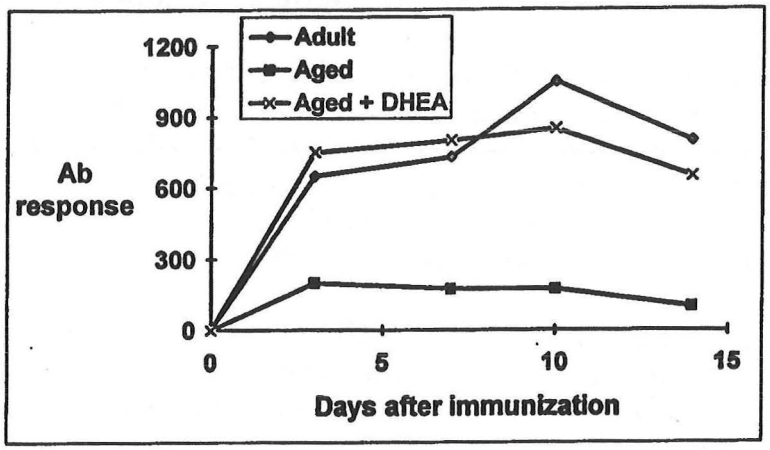
Although a limited number of serotypes have shown antimicrobial resistance at this time, however, there is no reason to predict that others will not do so soon. Serotypes that cause disease in one location are frequently different from the disease-associated serotypes in other places (81). Many serotypes cause disease worldwide:

WHO Collaborating Centre, 1992 (82) (includes PCN-susceptible isolates)
Children: 6A + 6B, 14, 18C, 19F, 7F, 23F, 19A (64.4% of the total isolates from invasive disease)
Adults: 3, 1, 14, 7F, 4, 6A + 6B, 8, 23F, etc. (17 types to cover 80%)

So the prospect for controlling penicillin-resistant pneumococci by vaccination using the currently formulated heptavalent vaccines is better for certain places (e.g., the U.S.) than for others.

**DHEA** (83,84) As mice age, their T cells lose the normal (mature adult) responses to stimulation. The steroid hormone dehydroepiandrosterone (DHEA) appears to restore the normal T cell response pattern. Daynes and colleagues (84), noting that the production of DHEA also decreases with age, asked whether administration of DHEA to senescent mice could increase their ability to produce

antibodies to hepatitis B surface antigen or ovalbumin. The results were dramatic. DHEA sulfate or DHEA, administered either topically or with the vaccine, greatly augmented antibody responses in the senescent mice. Similar results were obtained by Garg and Bonada using pneumococcal polysaccharide vaccine (83); this result is somewhat surprising, since polysaccharides are T-independent antigens. Regardless of the molecular mechanism, these studies raise the interesting possibility that simple hormonal manipulation could greatly increase the efficacy of immunization in the elderly.




(Effect of oral DHEAS on antibody responses of aged mice to ovalbumin, from Daynes and Araneo (84).)

**Does pneumococcal vaccine reduce the nasopharyngeal carriage of pneumococci?**

The ability of pneumococcal vaccination to decrease the carrier state has been studied infrequently. The most-cited data are from the pentavalent vaccine trial carried out by MacLeod and colleagues in the 1940's (85). They found that immunized military recruits had significantly lower rates of pneumococcal carriage than unimmunized recruits. In fact, the rates of carriage of vaccine-type *S. pneumoniae* were also reduced, relative to usual levels, in the unimmunized recruits, and they speculated about the impact of herd immunity in the overall population.

Several studies of meningococcal polysaccharide vaccination of military populations also found that immunization decreased nasopharyngeal carriage of the vaccine type *N. meningitidis* (86). While the *Haemophilus influenzae* type b polysaccharide vaccine did not reduce carriage in vaccinated children, the polysaccharide-conjugate vaccine may do so (87,88). A recent analysis by Dr. Trudy Murphy and her colleagues found that the *H. influenzae* polysaccharide conjugates vaccines were associated with 50 - 80% reduction of nasopharnygeal

carriage in day care children who received the vaccines (87). One may be optimistic that pneumococcal conjugate vaccines will have a similar impact.

No data are available regarding the ability of vaccination to prevent spread of pneumococcal infection from patients to hospital personnel.

**Can the use of pneumococcal vaccine be increased?**

Pneumococcal vaccine is not widely used in the U.S. at the present time (61). One strategy to increase the use of the vaccine has been to immunize at-risk patients who are hospitalized (89,90). Most patients with bacteremic pneumococcal disease have underlying conditions for which they are hospitalized prior to the pneumococcal episode (90). A deliberate program to vaccinate such persons before hospital discharge can greatly increase the use of the vaccine in the population at high risk of disease (89).

The best way to increase vaccine usage, however, would be to produce an unambiguously effective vaccine.

**Summary: pneumococcal vaccine**

1. The existing 23-valent polysaccharide vaccine is clearly not satisfactory for infants, children, or adults. Nevertheless, until a superior vaccine is produced, it is not unreasonable to use this vaccine according to the CDC guidelines listed above. An exception may be the severely immunocompromised, for whom vaccine efficacy has not ever been shown (68).

2. The optimal interval for booster doses is not clearly defined; many experts recommend every 5 or 6 years. The costs and benefits of this practice should be studied.

3. Some have suggested that all persons $\geq$ 55 years of age receive pneumococcal vaccine, since it is more immunogenic in younger persons. There is very little invasive pneumococcal disease in individuals who are between 55 and 65 years of age, however, outside the recognized high-risk groups (57).

4. Adults who live in crowded, confined quarters should probably be vaccinated, regardless of age or underlying medical condition.

5. *An effective pneumococcal vaccine is desperately needed. Resources should be directed toward developing the conjugate vaccines as quickly as possible.*

*An effective pneumococcal vaccine, even if used initially only in children, could help control the problem of penicillin resistance:*

*a) Since penicillin-resistant strains are more prevalent in pediatric populations, reducing the spread of these strains would reduce the transfer of the resistance genes to other bacteria.*

*b) Reducing the incidence of otitis media would reduce the use of antibiotics in children, thereby reducing the selective pressure that favors penicillin-resistant strains.*

*c) Since some adults acquire pneumococcal strains from children, there should be some reduction in the frequency of penicillin-resistant disease in adults. The similarity of penicillin-resistant serotypes in adults and children in the U.S. supports this notion.*

**Hospital infection-control strategies**

**Should patients with penicillin-resistant pneumococci be isolated in the hospital? Should contacts be given chemoprophylaxis?**

In several early reports, cases clustered in pediatric hospitals (and on wards within those hospitals), and carriage rates were high among patients who did not have clinically definable pneumococcal disease (2). Spread to (adult) hospital personnel was much less common.

In an overcrowded pediatric ward in a Johannesburg hospital where many children with measles were being treated, acquisition of resistant pneumococci was estimated to occur in 96% of previously culture-negative children within 3 days. In a less crowded hospital where fewer children carried resistant pneumococcal strains, the carriage acquisition rate was considerably lower (15% over 3 days) (3). Interestingly, spread of resistant pneumococci from children who were discharged from the hospital to their family contacts was minimal (3,91), and even spread from a carrier to other children living in an overcrowded orphanage was infrequent.

In the early years of the South African epidemic, efforts were made to control the epidemic by identifying and isolating carriers of resistant pneumococci. Only 4 resistant organisms were isolated from 264 patients with pneumococcal disease during the 2 years of this effort, vs. 48 resistant isolates from 194 patients with systemic infections in wards where these precautions were not taken. The control program was abandoned when resistance emerged to rifampin, one of the agents used to eradicate pneumococcal carriage in those whose cultures were positive (3).

An attempt to eradicate pneumococcal carriage in a day care center in the U.S. was transiently successful (63). The penicillin-resistant pneumococcal strain was susceptible to erythromycin and rifampin, so these drugs were given to all

children and staff for 7 days. Nasopharyngeal carriage of the resistant strain was eliminated over the course of the next month, but 16 weeks after the therapy 36% of the children were culture positive. Others have experienced similar difficulties with pneumococcal eradication in day care centers (63).

Conclusion: there is no good evidence that either patient isolation or chemoprophylaxis can prevent spread of pneumococci among hospital personnel and patients. This issue should be studied.

## CONCLUSIONS, RECOMMENDATIONS

**Therapy:** 1) Continue current practices for treating presumed pneumococcal infections other than meningitis. Perform cultures to assist management. Follow patients carefully and respond promptly to treatment failure by increasing the dose or switching antimicrobials based on sensitivity tests. For seriously ill, hospitalized patients, high dose therapy with penicillin G, other penicillins, or third-generation cephalosporins such as cefotaxime, ceftriaxone, or cefuroxime should be effective. If the patient's pneumococcal isolate is penicillin-sensitive in vitro, use penicillin--drug resistance is not the explanation for treatment failure in such cases.

2) Use vancomycin or cefotaxime for pneumococcal meningitis. The meningeal dose of vancomycin is 50 mg/kg/day in patients with normal renal function (do not exceed 4 grams/day). May combine either drug with rifampin (300 mg q8h). If the pneumococcal isolate is penicillin-sensitive, stop the empiric regimen and use high-dose penicillin. Be aware that neither vancomycin nor cefotaxime has been uniformly successful for treating pneumococcal meningitis. Repeat lumbar puncture 48 hours after initiating therapy to assess progress. Obtain pharmacokinetic consultation to assist with vancomycin dosing.

3) To reduce risk of inducing vancomycin resistance in hospital flora, avoid oral administration of vancomycin. In general, use metronidazole to treat antibiotic-induced colitis. Limit empiric use of vancomycin to well-established indications.

4) Encourage manufacturers to increase research efforts to find effective alternative antimicrobials.

**Prevention**: 1) Vaccinate members of high-risk groups in the community, including prisoners, homeless persons who live in shelters, and nursing home residents. Consider an institutional policy to vaccinate eligible patients at the time of hospital discharge.

2) Administer influenza vaccine annually to high-risk individuals (to prevent post-influenza pneumococcal pneumonia).

3) Consider (study) isolating patients with pneumonia for 48 - 72 hours to prevent spread of resistant pneumococci to hospital personnel.

4) Increase pressure on manufacturers to produce effective pneumococcal conjugate vaccines for adults and children.

5) Consider carefully the indications for each course of antimicrobial prescribed!

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