RESISTANCE: EFFECTIVENESS OF CURRENT INTERVENTIONS

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ABSTRACT

There is a demonstrated link between antibiotic resistance and the overuse of antibiotics. In addition, antibiotic misuse, such as the use of an inappropriate antibiotic or patients failing to complete their therapy, may also promote antibiotic resistance. Strategies are needed to tackle current and expected levels of resistance and to slow the development of antibiotic resistance. The 2 main strategies to address resistance are the development of new antibiotics that target resistant bacteria and better clinical practice. To encourage pharmaceutical companies to develop new antibiotics, it will be necessary to use economic incentives, such as the BioShield 2 "wild card" scheme, and improve the regulatory environment. Better clinical practice includes improved diagnosis of bacterial and viral infections; use of the appropriate antibiotics in situations in which there is proven benefit, through the use of guidelines or protocols; and promotion of patient compliance. Vaccine may be an effective strategy for some resistant organisms. The 7-valent pneumococcal conjugate vaccine has had a major effect in reducing resistant pneumococcal infections in children, and herd immunity has helped protect unvaccinated children and adults.

However, there are still concerns about increases in disease caused by nonvaccine serotypes, particularly 19A, which mean that appropriate antibiotic use programs are still vital.


As discussed in the first 2 articles of this monograph, there is a link between antibiotic resistance and antibiotic overuse and misuse. This article will address strategies to tackle current and expected levels of resistance and to slow the development of antibiotic resistance.

APPROPRIATE USE OF ANTIBIOTICS: SUCCESS OF CURRENT STRATEGIES AND FUTURE DIRECTIONS

The Infectious Diseases Society of America (IDSA) Committee on Antibiotic Availability has expressed concern about resistance in 3 main areas: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterobacteriaceae (VRE), Pseudomonas aeruginosa, Staphylococcus aureus USA 300 extended-spectrum β-lactamase, and acinetobacter in the United States; tuberculosis, malaria, and avian flu internationally; and anthrax and smallpox as bioterror agents. Although the IDSA's antibiotic resistance concerns are particularly targeted to the pathogens that are important in hospital infections, the resistance issue is also relevant to community-acquired respiratory tract infections (RTIs) and, as already outlined, increasing resistance among the gram-negative respiratory pathogens is a problem in clinical practice.

There are 2 main strategies to address this issue—development of new antibiotics that target resistant bacteria and better clinical practice.
**ANTIBIOTIC DEVELOPMENT**

Despite the concerns about resistance, the antibiotic pipeline is almost empty—big pharmaceutical companies are leaving the antibiotic field and only 1.5% of new molecular entities are antibacterial drugs, none of which are targeted at resistant gram-negative bacteria. Most commercial antibiotic research is directed at gram-positive cocci, driven by MRSA and VRE. The reasons are obvious—it costs $1 billion to develop a new drug and these costs may not be recouped. Antibiotics do not offer a particularly good return on investment; for the most part they are used acutely, for only 1 to 2 weeks, unlike the lifetime use of drugs for chronic diseases, and infectious diseases experts discourage their use to prevent development of resistance.

Biotechnology companies currently carry out most of the work in new antibiotic development. Unfortunately, the large pharmaceutical companies, not the smaller biotech companies, have the skill and economic resources to develop new drugs efficiently, thus if the current situation continues, it may take much longer to get new antibiotics to market and be less efficient than for other classes of drugs. Incentives, economic and regulatory, may help.

Economic incentives have the highest probability of succeeding. These include the Bioshield 2 “wild card,” which would allow companies to extend the patent on another US Food and Drug Administration (FDA)-approved drug of the company's choice, in return for developing a new antibiotic targeting a resistant strain. Another option is a more general patents extension for new antibiotics developed to target resistant bacteria, thus patent protection could last for 20 years from approval, rather than 20 years from patent submission.

The US FDA's regulatory environment can also provide a disincentive to investment in development of drugs for which there is not a large market or obvious return on investment. Pharmaceutical companies need to be informed of all changes in the US FDA rules and procedures. For example, the US FDA needs to provide a protocol for what it takes to obtain approval of a new drug for a particular disease, to be more open to change protocols, and accept applications that were based on best practice at the time the trials were conducted.

**BETTER CLINICAL PRACTICE**

There are various aspects to reducing antibiotic resistance through improved clinical practice—better diagnosis of bacterial infections; antibiotic discipline in prescribing, alternative prescribing practices, guidelines, and better selection of antibiotics; and promoting patient compliance with antibiotic regimen.

To choose the most appropriate antibiotic in any situation, it is important to understand the tangible benefits of each antibiotic for a given disease condition. The US FDA wishes to see placebo-controlled trials for any new antibiotics or indications. For example, placebo trials have been shown some interesting results: of the 18 available placebo-controlled trials for sinusitis, 16 show no significant benefit with antibiotic treatment. According to Cochrane reviews, antibiotic therapy reduces the duration of cough in bronchitis by 0.6 days. For acute exacerbations of chronic bronchitis, the US FDA would like to have a trial of doxycycline versus levofloxacin versus placebo. However, for meaningful results, large numbers of patients must be included, and this will be expensive to complete. Pharmaceutical companies are reluctant to run these types of trials, and are asking for help from other agencies.

Much antibiotic prescribing for RTIs is empiric because it is difficult to identify the causative pathogens. Templeton et al managed to identify the pathogen in 74% of 105 patients with community-acquired pneumonia (CAP), using multiplex real-time polymerase chain reaction (PCR) for atypical bacteria and respiratory viruses combined with conventional serology techniques. Microbiological diagnoses were determined for 52 (49.5%) patients by conventional techniques and for 80 (76%) by PCR, which was significantly more sensitive for detection of atypical pathogens and viruses (P ≤ 0.001). The most common pathogens were Streptococcus pneumoniae (22), rhinovirus (18), coronavirus (14), influenza virus (12), and Mycoplasma spp (10). However, PCR is not an inexpensive technique and there are no standardized, convenient, and reproducible tests for all common respiratory pathogens. In addition, there are issues around the ability to identify dual infections (bacteria and virus).

As discussed in the article by H. Goossens, MD, PhD, and Marc Lipsitch, MD, the Netherlands has the lowest use of antibiotics and the lowest rates of resistance in the European Union. Less than 2% of S. pneumoniae isolates are penicillin resistant, less than 2% of P. aeruginosa isolates are resistant to ceftazidime, cefepine, ciprofloxacin, or tobramycin, and there is a “search and destroy” policy toward MRSA. Prescribing
practices in the Netherlands are very different from those in the United States—upper RTIs are very rarely treated with antibiotics, CAP is always treated, and there is a “watch and wait” approach to pediatric acute otitis media, under which antibiotics are only used if the disease does not resolve itself.

Treatment guidelines for infectious diseases have been produced by various organizations, such as the Federal government, healthcare plans, professional societies, and expert groups. Their recommendations are evidence based, and they do offer many advantages. However, in some cases, the evidence on which they are based is questionable. In addition, before they can be implemented, guidelines must be widely disseminated to their target users. To ensure that the recommendations of the guidelines are sound, and that there is compliance with such recommendations, performance needs to be measured against guidelines. Furthermore, there must be some consequence for not complying with the recommendations, such as public notification of hospitals that do not comply or payment for performance. From a more positive angle, hospital treatment protocols could be developed that include good practice.

As a caveat to the discussion so far, Livermore has found that there is little evidence for any reduction in resistance following falls in antibiotic prescribing, and several pathogens (especially Escherichia coli) are becoming markedly more resistant. Therefore, it is important to use the antibiotics that are less prone to select resistance, rather than be overly optimistic about the benefits of reducing antimicrobial prescriptions. Guidelines should not be too narrow, railroading prescribing and its contingent selection pressure in one direction, as happened with gonorrhea. For example, cephalosporins lead to development of resistance through the acquisition by enterobacteriaceae of extended-spectrum β-lactamas and select for VRE, whereas fluoroquinolones lead to multidrug resistance. It is likely that limited diverse prescribing may have the least detrimental effect on resistance ecology.

Once the appropriate antibiotic is prescribed, it is important that the patient follows the correct regimen. Research in HIV medicine shows that there is a relationship between compliance and pill burden (when the number of pills is large), number of doses a day (twice vs 3 times daily), and directly observed therapy (including daily injection). Practice sessions, training sessions, and specialist staff have no benefit, whereas cognitive behavioral intervention has a small benefit over a limited period of time.

Targeting pneumococcal disease and even viral disease through the use of pneumococcal and viral vaccines may reduce the need for antibiotic prescribing.

**IMPACT OF NEW VACCINES AND VACCINATION STRATEGIES**

Vaccination may also prevent infections caused by resistant organisms. Prevnar (Wyeth Lederle Vaccines) is a 7-valent pneumococcal conjugate vaccine (PCV7) that contains 7 specific antigens, which are surface poly- or oligosaccharides, for 7 specific pneumococcal serotypes—4, 6B, 9V, 14, 18C, 19F, and 23F. Each antigen is individually conjugated to a carrier protein, the diphtheria CRM197 protein. Although there are 90 pneumococcal serotypes, the 7 used in the PCV7 are the major ones in the United States, causing more than 80% of invasive disease in children and approximately 50% to 60% in adults at the time the vaccine was licensed.

The conjugate vaccine was licensed in the United States in February 2000 for use in children. Recommendations for its use were published mid to late 2000, after which clinicians began using it. Vaccine shortages occurred from August 2001 to May 2003 and February to September 2004, but since then the supply has been stable. Vaccination with PCV7 is currently recommended for all children younger than the age of 2 years and those aged 2 to 4 years with certain chronic illnesses or compromised immunity.

**EFFECT ON PNEUMOCOCCAL DISEASE**

Several trials using different vaccines (4- to 9-valent) have shown that pneumococcal conjugate vaccination reduces carriage of vaccine serotypes. Most of these trials also found an associated increase in carriage of nonvaccine serotypes, resulting in no change in overall carriage rates. Thus, vaccination does not decrease overall pneumococcal carriage or transmission, but rather shifts the prevalent serotypes. Therefore, for conjugate vaccine that only covers selected serotypes to reduce overall disease, types included in the vaccine must be more capable of causing disease than nonvaccine types.

Several clinical trials show that vaccination is very effective against invasive pneumococcal disease and
pneumonia due to vaccine-type strains. PCV7 was used in Californian infants and Navajo and Apache children younger than 2 years old, whereas PCV9 was used in African infants in South Africa and the Gambia.10-13 Vaccination prevented 65% of invasive infections in HIV-positive children in South Africa, but as much as 97% of those in Californian infants, and 20% to 37% of chest X-ray–confirmed pneumonia among the 4 studies.10-13 In their study among children in the Gambia, Cutts et al showed that vaccination reduced overall mortality rates by 16%.13

In addition to the trials, various surveillance studies show a decline in invasive disease after the vaccine was introduced. For example, there was a decrease in invasive pneumococcal disease among adult and pediatric members of Northern California Kaiser Permanente; a reduction in pediatric hospitalizations for invasive pneumococcal disease in a network of 8 pediatric hospitals; a fall in pneumonia and respiratory tract diagnoses in children in Tennessee and New York; and a decline in invasive disease in US elderly.10,14-16

The Centers for Disease Control and Prevention (CDC) has also been tracking the effect of vaccination on invasive disease, mainly through Active Bacterial Core surveillance (ABCs), part of its Emerging Infections Program. ABCs is a population-based system that operates in various counties in Oregon, California, Minnesota, Georgia, Maryland, Connecticut, New York, Tennessee, Colorado, and New Mexico. Data for 1998 to 2003 show that rates of vaccine-type invasive disease among children younger than the age of 5 years fell significantly from approximately 80 cases/100,000 before to approximately 5 cases/100,000 after the introduction of PCV7 vaccination (Figure 1).17 This shows that disease caused by vaccine-type pneumococci is almost disappearing in young children. The data also show the important effect of herd immunity; in other age groups, who had not been vaccinated, disease caused by vaccine-type pneumococci was reduced by 50% to 65%. This demonstrates that children are a major source of pneumococcal infection in adults.

**EFFECT ON RESISTANCE**

It is clear that vaccination works very well against pneumococcal disease, especially the serotypes covered, but can a vaccine that effectively prevents disease based on targeting certain capsule types reduce antibiotic resistance?

Data are available for the levels of resistance prevalent among pneumococci before the introduction of PCV7 vaccination. CDC surveillance data show that there were only low levels of intermediate penicillin resistance among *S. pneumoniae* isolates in the 1980s, thus surveillance was stopped between 1988 and 1991 (Figure 2).18,19 When surveillance was resumed in the early 1990s, fully resistant strains had emerged and the resistance continued to increase until about 1999. An analysis of geographic diversity and temporal trends in

![Figure 1. Rates of Vaccine-Type Invasive Disease by Age Group Before (1998–1999) and After (2002–2003) Introduction of the Pneumococcal Conjugate Vaccine](image1)

![Figure 2. Penicillin Resistance in Streptococcus pneumoniae in the United States, 1979–1999](image2)
antimicrobial resistance among *S. pneumoniae* in the United States that used a mathematical transmission model and ABCs data demonstrated that, “… by July 2004, in the absence of a vaccine, 41% of pneumococci will be dually resistant (to penicillin and erythromycin), with 6% resistant to penicillin only and 4% to erythromycin only.” The model indicated that there was no sign of any slowing or leveling off in the increase of resistance.

PCV7 covers the serotypes that accounted for the greatest proportion of cases, as well as for most of the penicillin-resistant serotypes causing invasive disease, in the United States before its introduction. Data for 1999 from the ABCs shows that 5 of 7 serotypes cause most resistant infections (Figure 3). Of the nonvaccine-type strains, only 2 are important in terms of resistant disease. Thus, there is a close association between serotype and resistance in the United States, and this is also seen worldwide. Data from the Pneumococcal Molecular Epidemiology Network (PMEN), established in 1997 for global surveillance of antibiotic-resistant *S. pneumoniae* and to standardize names and classification of highly resistant strains, also show a relationship between vaccine type and resistance. To be listed in PMEN, a clone must be widespread and established (ie, it must be documented from >1 site over several years). PMEN currently lists 26 international clones, 18 of which are PCV7 vaccine types, 1 is vaccine-related, 4 are 19A serotype (not covered by the vaccine), and 3 are other serotypes.

Vaccination has a herd/transmission effect on carriage of resistant strains. A study of carriage of antibiotic-resistant pneumococci in daycare center attendees and their unvaccinated younger siblings showed that, as expected, vaccinated children had a significantly reduced risk of carriage of resistant strains. However, the younger siblings also had a significantly reduced risk of carriage of resistant *S. pneumoniae*.

Vaccination has also been shown to prevent invasive disease caused by resistant organisms. Klugman et al assessed the effect of a 9-valent pneumococcal conjugate vaccine (PCV9) in children with or without HIV in a randomized, double-blind trial in South Africa. A total of 19 922 children were vaccinated at 6, 10, and 14 weeks, whereas 19 914 received placebo. In children without HIV, vaccination reduced invasive pneumococcal disease by 83% and pneumonia by 20%, whereas in HIV-positive children, vaccination reduced invasive pneumococcal disease by 65%. Overall, the incidence of a first episode of invasive pneumococcal disease caused by penicillin-resistant organisms was reduced by 67%, whereas that caused by trimethoprim/sulfamethoxazole (TMP/SMX)-resistant strains decreased by 56%.

There are now data from actual clinical use rather than controlled clinical trials, some from the ABCs. Tennessee is one of the areas with the highest rates of resistance in the country, especially in young children. Surveillance for invasive pneumococcal disease in 5 Tennessee counties from 1995 to 2002 showed a massive decline in invasive disease in children younger than 2 years old, from 235 cases/100 000 to 46/100 000. In the same period, the proportion of cases caused by penicillin-nonsusceptible strains fell from approximately 60% to approximately 30%. Decreases were also seen in other age groups and for cephalosporin and erythromycin resistance.

Stephens et al studied the incidence of macrolide-resistant pneumococcus in Atlanta, Georgia. They found the biggest decreases where the vaccine is targeted, in children younger than 2 years old (82%) and 2 to 4 years old (71%). However, they also found a large decrease in adults, ranging from 25% to 54% depending on age. This is further evidence that children are a major source of pneumococcal disease in the community, and vaccinating them provides herd immunity. Interestingly, the clone that causes much of

**Figure 3. Distribution of Pneumococcal Serotypes by Frequency and Penicillin Resistance in US Children Younger than 2 Years Old in 1999**

Data from CDC.
the macrolide-resistant disease in Atlanta has a mefE-mediated mechanism for resistance and is a PCV7-type serotype 14. The decrease in macrolide-resistant pneumococcal disease was led by reducing circulation of this clone.

Active Bacterial Core surveillance data show that, even across sites, there has been a large drop in invasive disease caused by penicillin- and erythromycin-nonsusceptible and dual-resistant pneumococci since the introduction of PCV7 (Figure 4). From the peak in 1999 to 2003, the incidence of resistant disease fell by more than 80%. This effect appears to be largely due to the vaccine rather than other factors, such as more appropriate antibiotic usage. This is shown when ABCs data are examined by serotype: rates of penicillin-resistant disease in children younger than 2 years old caused by vaccine types fell from 57/100 000 in 1999 to approximately 2/100 000 in 2003, but over the same period, there was not much change in rates of resistant disease caused by vaccine-related and nonvaccine types. The prevalence of resistance seems to be improving among the smaller number of cases of invasive pneumococcal disease. In a study by Doern et al at 44 US medical centers, 1817 isolates from community-acquired RTIs in winter 2002 to 2003 were compared to earlier samples. The prevalence of resistance to β-lactams, macrolides, tetracyclines, TMP/SMX, and multiple drugs had reached a plateau or begun to decrease, although there was some increase in fluoroquinolone resistance.

**LONG-TERM PROSPECTS**

There is concern that widespread use of pneumococcal vaccination could lead to replacement disease. Removal of vaccine serotypes leaves a niche for nonvaccine serotypes or other organisms, such as *S. aureus*. The concern is that these new organisms may cause disease. Kaplan et al found significant replacement disease among children admitted to a network of 8 children’s hospitals. The authors tracked invasive disease in children younger than 2 years old between 1994 and 2002. Although there was a large decrease in invasive infections (66%) and those due to vaccine serotypes (77%), there was a significant increase in nonvaccine-type infections (66%). The largest increases were seen in infections due to serotypes 15 and 33, which are not typically resistant.

Data from the ABCs show that the largest increase in nonvaccine-type disease, particularly in children younger than 5 years old, is caused by serotype 19A pneumococci, which are often resistant (Figure 5). Before introduction of the vaccine (1999), 3 clones of 19A were found in children younger than 5 years, but after introduction (2003–2004), 2 of the original clones were joined by 6 new clones. Several of these new clones are typically found as vaccine-type strains.

**Figure 4. Rates of Invasive Disease Caused by Nonsusceptible Pneumococci Among Children Younger than 2 Years Old: ABCs 1998–2003**

![Figure 4](image-url)

**Figure 5. Rates of Invasive Pneumococcal Disease Caused by Serotype 19A: ABCs July 1999–June 2004**

![Figure 5](image-url)
which suggests that some strains may be able to pick up DNA to express a capsule that escapes the vaccine. This is cause for concern, especially as 19A is a resistant strain. Serotype 19A, in particular, may be increasing for several reasons: it is most commonly carried; the vaccine provides no cross-protection against 19A, even though 19F is an antigen in the vaccine; it is frequently antibiotic resistant, giving it a selective advantage; and some strains that were formerly PCV7 serotypes are able to acquire a nonvaccine (19A) capsule.

CONCLUSIONS

There are 2 main strategies to address resistance—development of new antibiotics that target resistant bacteria and better clinical practice. It will be necessary to use economic incentives, such as the BioShield 2 wild card scheme, and improve the regulatory environment to encourage pharmaceutical companies to develop new antibiotics. Better clinical practice includes improved diagnosis of bacterial and viral infections; use of the appropriate antibiotic in situations in which there is proven benefit, through the use of guidelines or protocols; and encouraging patient compliance.

Vaccination may also be an effective strategy for reducing infections caused by resistant strains. The 7-valent pneumococcal vaccine has had a major effect in reducing resistant infections in children, and herd immunity has helped protect unvaccinated children and adults. However, there are concerns about nonvaccine serotypes, particularly 19A, which means that appropriate antibiotic use programs are still vital.

REFERENCES


