Antibiotic Resistance in *Streptococcus pneumoniae*: What Does the Future Hold?

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The recent emergence of strains of drug-resistant *Streptococcus pneumoniae* (DRSP) is a serious clinical and public health problem. Several interventions have been proposed to limit the further emergence and spread of DRSP, including campaigns for appropriate antibiotic use and the introduction of pneumococcal conjugate vaccines. Whether the current epidemic of drug resistance in *S. pneumoniae* is sustainable or will succumb to current efforts to limit its spread will be decided by an interaction of factors related to the pathogen (i.e., the relative fitness of the resistant strains), to the prescription of antibiotic treatment (i.e., changes in selection pressure), and to the host (i.e., the ability to slow the transmission of DRSP). Much investigation is still needed to better ascertain how maintenance of DRSP strains in the community at large is influenced by each factor and affected by current interventions that are based on these factors.

*Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia, meningitis, and acute otitis media in the United States. The rapid emergence of strains of drug-resistant *S. pneumoniae* (DRSP) during the past 2 decades is, therefore, an important clinical and public health problem. In response to the problem, a number of professional and public health organizations have promoted interventions to reinforce appropriate antibiotic use and promulgated other strategies, such as vaccination, to limit the further spread of DRSP. Evidence is currently lacking, however, as to the likely impact of these interventions.

Is the current epidemic of DRSP carriage likely to succumb to current efforts to limit it? In the antimicrobial era, the outcome of infection is determined by the tripartite interaction between pathogen, antibiotic, and host. The same factors likely interact to determine whether drug resistance is maintained once it is introduced into a population. Mathematical models have been used to predict the future course of the epidemic [1] and the potential impact of interventions to reduce drug resistance, such as restriction of use of antibiotics [2]. These models must take into account a number of variables related to the pathogen (the growth rate differential between resistant and susceptible organisms), antibiotic use in the population (the magnitude of selective pressure applied over the population), and the host population (the rate of acquisition/transmission of infection or colonization) (table 1). Here we review the available evidence and assess the relative importance of pathogen, antibiotic, and host in the maintenance of DRSP strains in the community at large.

### PATHOGEN-RELATED FACTORS

The ecological niche for *S. pneumoniae* is the human nasopharynx. Carriage of pneumococci in the nasopharynx is more common in young children. The duration of carriage is influenced by host-related factors, such as age, and by pathogen-related factors, such as serotype. Although carriage is usually asymptomatic, it also serves as the chief source for invasive pneumococcal infections and for person-to-person transmission.

For most commonly used antibiotic classes (e.g., β-lactams and macrolides), acquisition of resistance genes by pneumococci results from transformation (i.e., in-
corporation of free DNA from related species in the nasalopharyngeal flora) or transfer of genes on conjugative transposons. De novo resistance to these antibiotics occurs only rarely in a susceptible population. This is in contrast to the predictable (provided the overall population size is adequate) occurrence of subpopulations with reduced susceptibility to fluoroquinolones because of spontaneous point mutations. Because β-lactam resistance is unlikely to arise within a given host, the acquisition of DRSP by an individual and the dissemination of DRSP within a population must occur through transmission and amplification of drug-resistant clones.

Although there are 90 serogroups of S. pneumoniae, most clinical isolates with high-level β-lactam resistance belong to serotypes 6B, 9V, 14, 19F, or 23F. These isolates often belong to clonal strains that have acquired resistance to multiple antibiotics and have been widely disseminated—throughout the world, in some cases. In the United States, for example, 70% of multidrug-resistant S. pneumoniae isolates belong to 1 of 9 clonal strains [3]. The reason that these serotypes are overrepresented among DRSP strains is not fully understood, but it may be that because these serotypes are more commonly carried by children and carried for longer durations than other serotypes, they are exposed to greater selective pressure resulting from the widespread use of antibiotics in this age group. Because the new conjugate vaccines target these serotypes, the implementation of use of these vaccines is expected to have an important role in limiting the spread of DRSP strains.

Natural barriers in genetic fitness could limit the spread of DRSP strains. Whether the common mechanisms conferring drug resistance come at a significant cost to the organism is debated. In the case of alterations in penicillin-binding proteins that confer β-lactam resistance in pneumococci, the close sequence homology of the various penicillin-binding protein genes suggests that such alterations could create a competitive handicap in bacterial fitness that becomes a survival advantage only if there is exposure to β-lactams. The fundamental question remains whether DRSP strains are able to compete with susceptible strains once the selective pressure of antibiotics is reduced or removed. It is commonly assumed that DRSP strains do not compete as well and will therefore recede in the absence of antibiotic exposure. This assumption has given rise to campaigns for more judicious use of antibiotics and is supported by the success of campaigns to restrict antibiotic use in Finland and Iceland [4, 5]. Indeed, both clinical isolates and laboratory-derived mutants with alterations in penicillin-binding proteins conferring resistance to penicillin have shown defective growth in drug-free medium [6] and reduced virulence in mouse models [7, 8]. However, to date, there is no convincing clinical evidence that the prevalent DRSP strains have reduced virulence. Whether DRSP strains might be less competitive at colonizing the nasopharynx (and therefore less transmissible) is even less well understood.

Nevertheless, transmission of DRSP and invasive infection do occur. It is possible that resistant bacteria selected in the clinical setting have acquired additional compensatory factors that restore virulence. This might occur if unfit mutants were able to survive in the nasopharynxes of children and immunocompromised adults long enough to regain virulence, allowing transmission and infection to proceed [9].

**Table 1. Factors likely to affect the sustainability of the epidemic of Streptococcus pneumoniae.**

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen-related</td>
</tr>
<tr>
<td>Natural barriers in genetic fitness</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td>Appropriate-use campaigns</td>
</tr>
<tr>
<td>Host-related</td>
</tr>
<tr>
<td>Pneumococcal vaccines</td>
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<tr>
<td>Influenza vaccines</td>
</tr>
</tbody>
</table>

**DRUG-RELATED FACTORS**

**Appropriate-use campaigns.** The association between community-wide use of antibiotics and the emergence of pneumococcal resistance has been demonstrated for β-lactams, macrolides, and fluoroquinolones [10]. Recent antibiotic use has been shown repeatedly to be the strongest risk factor for the carriage and spread of resistant pneumococci, at both the individual and the community levels [11]. It is also associated with invasive disease caused by DRSP [11].

In the individual, antibiotic use most likely selects for resistance in 1 of 2 ways: by unmasking, or selectively amplifying, resistant clones already present as a small proportion of the infecting or colonizing population, or by clearing out the normal nasopharyngeal flora and allowing replacement by a resistant strain circulating in the community during or after antibiotic therapy. There is support for the occurrence of both mechanisms, which may vary in relative frequency depending on the prevalence of DRSP carriage in the community [12].

The majority of antibiotic prescriptions in the United States (up to 75%) are for upper respiratory tract infections in ambulatory patients [13]. Many of these prescriptions are thought to be unnecessary because of the viral etiology of colds and acute bronchitis. Investigators from the Centers for Disease Control and Prevention (CDC) estimate that, if antibiotics were prescribed appropriately for upper respiratory tract infections, the number of antibiotic prescriptions would fall by >40% [14]. Because the prevalence of DRSP strains would be expected to...
systems is uncertain. In the United States, controlled studies of practices for ambulatory patients and in isolated rural communities, as well as in larger geographic groups, have shown that the number of antibiotic prescriptions can be reduced with focused interventions (table 2) [15–19]. The most successful interventions have targeted caregivers and the lay community, particularly parents of young children. However, only a few studies to date have addressed whether reduction in prescriptions is associated with isolation of fewer DRSP strains (table 2) [17–19]. Belongia et al. [17] reported a nonrandomized, controlled community intervention trial in Wisconsin in which an educational intervention targeting clinicians and parents resulted in intervention-attributable reductions of 11% and 23% in the rates of prescription of solid and of liquid antibiotics, respectively, within 1 year after the start of the intervention. However, no significant differences in the rates of antibiotic use or PNSP colonization could be demonstrated between children in child care facilities in intervention communities and those in and control communities. It is not surprising that carriage of PNSP in the postintervention period was associated with receipt of antibiotic treatment during the preceding 3 months, by a multivariate logistic regression model.

Hennessy et al. [18] performed a nonrandomized intervention trial in rural Alaska communities. The educational intervention targeted community health aides, regional physicians, and community residents and provided information on the nature of upper respiratory tract infections and appropriate antibiotic use for upper respiratory tract infections. After 6 months, the initial intervention involving only 1 community resulted in a 22% intervention-attributable reduction in the rate of antibiotic prescription, a finding associated with a 9% decline if such widespread selective pressure were reduced or removed, more appropriate use of antibiotics for upper respiratory tract infections has been recommended by a number of groups.

Clinical-outcome studies have addressed whether interventions to reduce prescription of antibiotics lead to declines in the prevalence of DRSP strains. Nationwide initiatives to reduce antibiotic use were instituted in Finland, to reduce macrolide resistance among group A streptococci, and in Iceland, to reduce penicillin resistance among pneumococci [4, 5]. In Finland, national guidelines for reducing outpatient use of macrolides resulted in a 42% reduction in the number of daily doses prescribed that was sustained for 5 years [4]. During a 5-year period, rates of macrolide resistance among group A streptococcal isolates fell by 48%, a decline that was not evident until 2 years after the release of the guidelines. In Iceland, a countrywide public health campaign targeting physicians and the public that began in 1990 resulted in a 9% reduction in the number of daily doses of antibiotics during a 4-year period [5]. The reduction in the number of prescriptions was associated with a 6% decline in penicillin-nonsusceptible S. pneumoniae (PNSP) isolates from 1993 to 1994, after years of steady increases. A 25% reduction in PNSP carriage in children attending day care centers was also noted during the 4-year period. It is remarkable that the number of antibiotic prescriptions was reduced primarily for macrolides and trimethoprim-sulfamethoxazole, not β-lactams. This finding reveals the potential for cross-selection of resistance by different antibiotic classes and reinforces the importance of reducing the use of all antibiotics, not just selected classes.

Whether the interventions promoted in Finland and Iceland would be successful in countries with decentralized medical

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration of intervention</th>
<th>Population studied</th>
<th>Reduction in no. of antibiotic prescriptions, %a</th>
<th>Change in rates of PNSP isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzales et al. [15]</td>
<td>4 months</td>
<td>Health management organization practices, Denver, Colorado</td>
<td>24o</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Finkelstein et al. [16]</td>
<td>1 year</td>
<td>Managed care organization practices, Massachusetts and Washington</td>
<td>12–16</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Belongia et al. [17]</td>
<td>4 months</td>
<td>Various practice models, Wisconsin</td>
<td>11–23</td>
<td>No significant changec</td>
</tr>
<tr>
<td>Hennessy et al. [18]</td>
<td>6 monthsd</td>
<td>Remote community, Alaska</td>
<td>22</td>
<td>9% Decrease</td>
</tr>
<tr>
<td>Hennessy et al. [18]</td>
<td>6 monthse</td>
<td>Remote communities, Alaska</td>
<td>25b</td>
<td>No significant changef</td>
</tr>
<tr>
<td>Perz et al. [19]</td>
<td>1 year</td>
<td>Knox County, Tennessee</td>
<td>11</td>
<td>No significant changeg</td>
</tr>
</tbody>
</table>

**NOTE.** PNSP, penicillin-nonsusceptible Streptococcus pneumoniae.

- a Intervention-attributable reduction in antibiotic prescription rate.
- c Effect of full intervention.
- b Initial intervention.
- d Nasopharyngeal isolates from children in child care facilities (no significant change in the rate of antibiotic prescription for this subgroup).
- f No control group for comparison.
- e Expanded intervention.
- g Isolates from blood, CSF, or other sterile sites.
Table 3. Pharmacokinetic characteristics of orally administered β-lactam antibiotics against *Streptococcus pneumoniae* with differing susceptibilities to penicillin.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;, µg/mL</td>
<td>Time &gt; MIC, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;, µg/mL</td>
</tr>
<tr>
<td>Cefitubuten</td>
<td>400 mg q.d.</td>
<td>4</td>
<td>29</td>
<td>8–64</td>
</tr>
<tr>
<td>Loracarbef</td>
<td>400 mg b.i.d.</td>
<td>0.5</td>
<td>50</td>
<td>2–16</td>
</tr>
<tr>
<td>Cefixime</td>
<td>400 mg q.d.</td>
<td>0.5</td>
<td>59</td>
<td>4–16</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>500 mg t.i.d.</td>
<td>0.5</td>
<td>60</td>
<td>8–16</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>300 mg b.i.d.</td>
<td>0.12</td>
<td>77</td>
<td>0.5–4</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>500 mg b.i.d.</td>
<td>0.12</td>
<td>75</td>
<td>0.5–2</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>500 mg b.i.d.</td>
<td>0.25</td>
<td>75</td>
<td>0.5–4</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>200 mg b.i.d.</td>
<td>0.25</td>
<td>83</td>
<td>0.25–2</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>400 mg b.i.d.</td>
<td>&lt;0.1</td>
<td>85</td>
<td>0.12–0.5</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg t.i.d.</td>
<td>&lt;0.1</td>
<td>100</td>
<td>0.25–1</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1 g t.i.d.</td>
<td>&lt;0.1</td>
<td>100</td>
<td>0.25–1</td>
</tr>
</tbody>
</table>

*NOTE.* Data from [20, 21], with the following exceptions: data for amoxicillin, 1 g t.i.d. dosage, from [22]; for cefitubuten, from [23, 24]; for cefdinir, from [25, 26]; and for cefditoren, from [25, 27].

*<sup>a</sup> Percentage of dosing interval during which serum concentrations exceeded the MIC.*

attributable reduction in the proportion of PNSP strains among nasopharyngeal isolates. When the intervention was expanded to multiple communities, however, no significant effect on PNSP carriage was demonstrated, despite similar reductions in the rate of antibiotic prescription in the new intervention communities. Indeed, in the initial intervention community 18 months from beginning the intervention, rates of PNSP isolation returned to preintervention levels, despite sustained reductions in the rates of antibiotic prescription.

Perz et al. [19] evaluated the impact of a broader community intervention in Knox County, Tennessee. Using the 3 other urban counties in Tennessee as control communities, the investigators found an 11% intervention-attributable decline in the rate of antibiotic prescription between the 12-month preintervention and postintervention periods but no change in the rates of resistance among invasive pneumococcal isolates. Resistance rates among nasopharyngeal isolates were not assessed.

Overall, these studies suggest that sustained reductions in the rate of antibiotic prescription for upper respiratory tract infections are possible with appropriate interventions. However, whether the achievable reductions can have a measurable and durable impact on resistance rates remains an open question. Although the results from the controlled intervention trials reviewed above appear discouraging, it is possible that insufficient time was allowed for measurable declines in resistance rates to take place. In the Finnish and Icelandic studies described above, measurable declines in resistant isolates did not appear for several years after the intervention [4, 5].

***Highly potent agents.*** The use of antibiotics, even for appropriate indications, will continue to exert selective pressure favoring drug-resistant strains. Therefore, it is important that antibiotic regimens be prescribed in a way that minimizes the risk of the emergence and spread of drug resistance. It seems intuitive that suboptimal exposure to an antibiotic (i.e., due to the use of agents with low antimicrobial potency, inadequate dosing regimens, and/or prolonged duration of inadequate therapy) may selectively reduce the population of susceptible bacteria and favor the selection and outgrowth of drug-resistant clones.

Unfortunately, too few studies have evaluated the relationships between the use of specific antibiotic agents or dosing regimens and the emergence of resistance in clinical studies. Pharmacokinetic and pharmacodynamic data from experimental models and clinical studies are increasingly being used to predict when suboptimal antibiotic exposure may occur. Specific pharmacokinetic and pharmacodynamic parameters have the ability to predict antimicrobial efficacy in experimental models and in human infections on the basis of serum concentrations achievable during therapy [20]. These parameters may then be used to compare agents within or between antibiotic classes, as well as different dosing regimens of the same agent, to determine their potential to eradicate both susceptible and resistant bacterial populations and to prevent the selection of resistant mutants.

For example, on the basis of pharmacokinetic and pharmacodynamic considerations (table 3), amoxicillin is the most active orally administered β-lactam against *S. pneumoniae*, achieving concentrations that should inhibit the growth of PNSP with penicillin MICs as high as 4 µg/mL [20, 21]. Many orally administered cephalosporins, on the other hand, achieve...
concentrations adequate to eradicate susceptible, but not non-susceptible, pneumococci, thereby strongly favoring the selective amplification of β-lactam-resistant strains. This hypothesis has been confirmed in comparative studies of amoxicillin and cephalosporins for treatment of acute otitis media [28, 29]. Amoxicillin was able to effectively eradicate both susceptible and nonsusceptible pneumococci from the middle ear and reduce the level of nasopharyngeal carriage, whereas the oral cephalosporins (cefuroxime, cefaclor, and cefixime) were less effective in eradicating PNSP from the middle ear and ineffective at eliminating PNSP carriage.

Similar arguments apply to the fluoroquinolone class, in which the agents most potent against S. pneumoniae are gatifloxacin and moxifloxacin. These agents are more likely to achieve target pharmacokinetic and pharmacodynamic parameters for the eradication of susceptible pneumococci and strains with first-step resistance mutations than are fluoroquinolones of lower potency, including levofloxacin [30, 31]. In the current era of rampant antibiotic overuse, the use of the most potent antibiotics in each class may be one of the most effective ways to limit the selective pressure favoring the emergence and spread of DRSP.

Short-course therapy. It has recently been suggested that shorter courses of therapy for upper respiratory tract infections are equally efficacious and also less likely to select for drug resistance. In support of this idea, several studies have found that short-course, high-dose β-lactam regimens are less likely to lead to carriage of PNSP after therapy than are longer courses of lower doses [32, 33]. However, whether the short course or the high dose has a greater influence on preventing the emergence of resistance cannot be determined from these studies. A randomized, double-blind, multicenter trial of 5 days versus 10 days of treatment with amoxicillin-clavulanate for acute otitis media failed to discern differences in levels of PNSP colonization after therapy [34]. Although short-course therapy is attractive for reducing community-wide antibiotic selective pressure and improving treatment adherence rates, these results, together with increasing evidence that bacterial eradication is important to clinical outcomes in acute otitis media [29], suggest that choosing potent agents and administering them at appropriate dosages is more important in preventing emergence of drug resistance in the individual patient [35].

Conclusion. Changes in antibiotic formularies and prescribing habits may have the potential to help limit the spread of DRSP. Studies with longer follow-up may be required to discern changes in rates of antibiotic resistance. More controlled studies designed to assess the changes in rates of DRSP carriage during and after therapy are also necessary before improved recommendations can be made regarding the agents and regimens that are least likely to select for resistant mutants. Information from pharmacokinetic and pharmacodynamic models should be integral in planning such studies.

HOST-RELATED FACTORS

Pneumococcal vaccine. The 23-valent pneumococcal polysaccharide vaccine (Pneumovax [Merck]) is 60%–70% efficacious in preventing invasive pneumococcal disease, although its efficacy varies depending on age and immune status [36]. Regarding its potential for limiting the spread of DRSP, this vaccine has 2 significant shortcomings. First, it is not effective for children <2 years of age, who represent a major reservoir of DRSP. Second, it does not prevent noninvasive pneumococcal infections, such as nonbacteremic pneumonia [37], or carriage of pneumococci, the latter being the major means of transmission of DRSP. Therefore, although improved vaccination rates might reduce the selection pressure that occurs when antibiotics are required to treat invasive pneumococcal infections, the potential for significantly reducing the rate of DRSP transmission is low.

Pneumococcal conjugate vaccines, on the other hand, such as the recently licensed product Prevnar (Wyeth Lederle Vaccines), hold promise for limiting the spread of DRSP while reducing the substantial morbidity and mortality due to pneumococcal infections in children. Five of the serotypes represented in the currently licensed 7-valent vaccine are highly associated with antibiotic resistance. Overall, ∼80% of PNSP infections are caused by serotypes included in the vaccine [38]. Furthermore, these vaccines succeed when the polysaccharide vaccine does not. They are immunogenic for infants and toddlers and immunocompromised children and are highly effective in preventing invasive disease due to serotypes included in the vaccine [39]. Although the effect is less impressive, the vaccines also protect against noninvasive infections, including acute otitis media [38].

Of primary importance when considering the impact on DRSP transmission, however, is the fact that the vaccines have demonstrated efficacy in reducing the rate of carriage of vaccine serotypes by ∼50% [38]. Thus, vaccination of children would be expected to have a herd effect on the population, whereby the rate of acquisition of vaccine (i.e., antibiotic-resistant) serotypes is reduced, even among the unvaccinated fraction of the population. The impact on the rate of carriage of nonvaccine serotypes has been mixed, however; some studies have shown an increase in carriage rates among unvaccinated subjects (table 4). Whether this is due to replacement of vaccine serotypes with nonvaccine serotypes or due to unmasking of nonvaccine serotypes already present at low proportions is unclear. Replacement may be more common in settings with a high likelihood of pneumococcal transmission, such as child day care centers.
Use of the vaccines should also reduce antibiotic use, because much of the empirical use of antibiotics to treat febrile children targets occult pneumococcal infection. In an Israeli study of a 9-valent conjugate vaccine, vaccination was associated with a 15% reduction in the number of courses of antibiotics received, compared with a control group that received a meningococcal vaccine [48]. Once the efficacy of the vaccine is well accepted, empirical use of antibiotics to treat children with fever of unknown etiology should decline.

An analysis by Feikin and Klugman [49] has demonstrated a shift in the serotypes causing invasive pneumococcal disease during the last century, whereby the so-called “epidemic” serotypes (1, 2, 3, and 5) have been replaced by serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The serotypes in the latter group are carried more frequently and for longer durations in children than are the serotypes in the former group. The advent of antibiotic therapy in the mid-20th century (together with improved socioeconomic conditions and other factors) apparently succeeded in interrupting the epidemic transmission cycles of serotypes in the former group while providing selective pressure that more readily favored survival of strains with a greater propensity for carriage in the nasopharynx. The prolonged carriage increased the likelihood that strains acquiring antibiotic resistance would be presented with a selective advantage in the form of antibiotic exposure. The selective pressure of the conjugate vaccines will now be tested through mass vaccination campaigns. Will nonvaccine serotypes replace vaccine serotypes in the nasopharynx? If so, will they have similar capacity for invasive disease, person-to-person transmission, and antimicrobial resistance? Even if nonvaccine serotypes have reduced capacity for invasive disease, do they have reduced capacity for noninvasive diseases, such as acute otitis media?

Concern has arisen regarding the potential impact of serotype switching, whereby virulent DRSP strains of vaccine serotypes (e.g., the globally transmitted multidrug-resistant clones of serotypes 6B, 9V, and 23F) undergo recombination events that result in the expression of the capsular polysaccharide of nonvaccine serotypes [12, 50]. If the carriage of nonvaccine serotypes increases with mass vaccination, the potential for such serotype switching also increases. Thus, the selective pressure of an effective vaccine could interact with the selective pressure of antibiotic therapy to produce multidrug-resistant clonal strains that are highly efficient in transmission, have increased virulence, and now belong to a serotype that is not covered by the vaccine. The impact of capsular switching on virulence and transmissibility remains unanswered, but capsular transformation of a multidrug-resistant serotype 23F clone to serotype 3 has been demonstrated to occur, with an associated increase in virulence [50].

Recent data from the Active Bacterial Core Surveillance program of the CDC demonstrate that the introduction of the conjugate vaccine has been associated with a reduction in the rate of invasive pneumococcal disease in children, including a 69% reduction among children <2 years of age [51]. A more modest reduction in invasive disease was also noted among adults. Moreover, the overall rate of invasive infections caused by penicillin-non-susceptible pneumococci fell by 35%. These data are corroborated by a trial of a conjugate vaccine in children with and without HIV infection that showed reductions of 67% and 56% in the incidence of disease caused by penicillin-resistant and trimethoprim-sulfamethoxazole–resistant strains, respectively [52]. Together, these findings suggest that the vaccine may be an effective new tool for reducing disease caused by DRSP strains.

Given these promising new data, there exists now a great opportunity (and an equally great responsibility) to actively monitor the impact of these vaccines on the rate of carriage of DRSP strains and of nonvaccine strains. Although the restricted range of serotypes included in the various formulations may ultimately limit the utility of current conjugate vaccines,

Table 4. Effect of pneumococcal conjugate vaccines on rates of nasopharyngeal carriage of drug-resistant *Streptococcus pneumoniae.*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study location</th>
<th>No. of serotypes in vaccine</th>
<th>Vaccine serotypes</th>
<th>Nonvaccine serotypes</th>
<th>All serotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obaro et al. [40]</td>
<td>The Gambia</td>
<td>5</td>
<td>Reduction</td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>Dagan et al. [41]</td>
<td>Israel</td>
<td>7</td>
<td>Reduction</td>
<td>No change</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Dagan et al. [42]</td>
<td>Israel</td>
<td>4</td>
<td>Reduction</td>
<td>No change</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Mbelle et al. [43]</td>
<td>South Africa</td>
<td>9</td>
<td>Reduction</td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>Obaro et al. [44]</td>
<td>The Gambia</td>
<td>9</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Dagan et al. [45]</td>
<td>Israel</td>
<td>9</td>
<td>Reduction</td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>Givon-Lavi et al. [46]</td>
<td>Israel</td>
<td>9</td>
<td>Reduction</td>
<td>Increase</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Dagan et al. [47]</td>
<td>Israel</td>
<td>9</td>
<td>Reduction</td>
<td>Increase</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from Whitney [38].
these vaccines should be considered foundations for the addition of new capsular polysaccharides to widen coverage as deemed necessary after a period of surveillance.

Influenza vaccine. Although influenza vaccination does not target S. pneumoniae directly, improved vaccination rates might indirectly assist in controlling the spread of DRSP. A reduction in the incidence of influenza is likely to reduce the population-wide selection pressure that results from inappropriate use of antibiotics for influenza. This benefit would be compounded if influenza vaccination prevented secondary pneumococcal infection. Secondary bacterial pneumonia, most commonly due to S. pneumoniae, is a well-known complication of influenza. If improved vaccination rates were to reduce the incidence of pneumonia and invasive disease due to S. pneumoniae, the need for antibiotic therapy and the attendant increase in selection pressure would be reduced. A recent prospective study from Sweden examined the effectiveness of influenza and/or pneumococcal vaccination in preventing hospitalization and death due to influenza, all-cause pneumonia, pneumococcal pneumonia, and invasive pneumococcal infection [53]. Influenza vaccination alone did not protect against pneumococcal disease during the first 6 months of the study, although the findings were limited by the fact that outcomes were assessed only among hospitalized patients [53]. Thus, the impact of influenza vaccination on the prevalence of DRSP strains, although anticipated on clinical grounds, remains unproven epidemiologically.

WHAT DOES THE FUTURE HOLD?

We are still at an early point in our awareness of and our response to the epidemic of pneumococcal drug resistance. Predictions about the future course of the epidemic and the overall effectiveness of interventions intended to limit its evolution are currently difficult to make. Still, the cost of doing nothing would likely be severe. Using active surveillance data on invasive pneumococcal infections at 8 sites in the United States during 1996–1999, McCormick et al. [1] predict an actual decline in the number of isolates resistant to penicillin alone between 1996 and 2004 and a rather small increase in erythromycin resistance during the same period. These benign predictions, however, are overwhelmed by the alarming projection of a nearly 5-fold increase (from 8.6% to 40.6%) in the prevalence of isolates dually resistant to penicillin and erythromycin [1].

Are current interventions having any large-scale impact on the rate of pneumococcal drug resistance? Antibiotic prescription rates for some upper respiratory tract infections in children <15 years of age are declining in the United States [54], and there is preliminary evidence from sources in Europe and North America that rates of reduced susceptibility to penicillin among pneumococci are stabilizing or even decreasing. Indeed, recent data from the Tracking Resistance in the United States Today Trust surveillance program suggest that rates of in vitro macrolide and penicillin resistance stabilized between 2000–2001 and 2001–2002 [55]. Hoban et al. [56] described a 20% decline in PNSP isolates between 1997–1998 and 2000–2001 in Canada that was commensurate with a 14% decrease in total antibiotic consumption. Furthermore, in Madrid, Spain, rates of penicillin and cefotaxime nonsusceptibility were stable during the period 1996–2000 [57], and data from the Alexander Project show stable rates of PNSP in Italy, Germany, and France during the period 1994–1998 [58] that was then followed by a significant decrease in macrolide and penicillin resistance among pneumococci during 1999–2000 [59]. Unfortunately, some of this apparent success may have come at the expense of resistance to other antimicrobial classes. The rates of fluoroquinolone resistance in these areas have not leveled off [25], a phenomenon probably related to increased use of this class of agents, largely driven by fear of penicillin and macrolide resistance [58, 60].

More-appropriate use of antibiotics and the introduction of the pneumococcal conjugate vaccines appear to offer the most promise for limiting the spread of drug resistance among pneumococci, but there is much more work to be done. Mathematical models predict that rates of resistance decay more slowly than they emerge [2]. Priorities for a sustained effort must include further widespread interventions to reduce global antibiotic consumption, protection of the effectiveness of antibiotic classes to which little resistance has emerged, and active surveillance of the serotypes and antimicrobial susceptibilities of nasopharyngeal isolates following the implementation of use of conjugate vaccines.

References


