Now that Dr. Wallace has told you about the reasons for the PCV shortage and its extent, I'd like to take a few minutes to describe CDC's recommendations for coping with the shortage and the process that led to these recommendations.

CDC's recommendations are intended to accomplish two objectives, the first is to conserve the national PCV supply by asking providers to defer, for now, the third and fourth doses of the routine, 4-dose series for healthy children. This simple measure should minimize the number of practices that run completely out of vaccine for more than a week or two and thus minimize the number of children who go completely unprotected for any significant length of time. The second objective is to provide guidance to clinicians to help them use their limited supplies to protect the children at greatest risk of serious *Streptococcus pneumoniae* infection.

In dealing with the current PCV shortage, we have the advantage of lessons learned from dealing with the first PCV shortage. In September 2001, less than 12 months after the ACIP had issued its initial recommendations for the use of PCV, the CDC announced a PCV shortage and in December of 2001, the ACIP issued "Updated Recommendations on the Use of Pneumococcal Conjugate Vaccine in a Setting of Vaccine Shortage." We learned three things during that shortage. We learned that vaccine supplies tend to be uneven, that is, some providers have plenty of vaccine while other are completely out of stock. We learned that providers' compliance with recommendations depended on their supply of vaccine. And we learned that people may have trouble following recommendations that they think are complicated.

This table presents the essentials of the ACIP's 2001 recommendation. Although the intention was to provide flexible recommendations that address nearly every situation an immunization provider might encounter, some providers felt that the recommendations were too complicated.

During the midst of the first shortage, from November 2002 to March 2003, a team led by Dr. Karen Broder of NIP surveyed pediatricians who provided immunization services. Questionnaires were sent to 2500 members of the American Academy of Pediatrics. Fifty-seven percent of the questionnaires were returned and 67% of those were from pediatricians who provided primary, outpatient pediatric care including PCV and were therefore eligible to be included in the survey.

We found that the supply of vaccine was uneven. Of nearly 1000 eligible respondents, 67% of respondents reported having been completely out of PCV for one month or longer yet 21% of providers reported having experienced no shortage in their practice at all. This finding demonstrated the importance of the careful allocation of limited vaccine supplies that Dr. Wallace mentioned. CDC and the manufacturer are working hard to allocate supplies equitably within the public and private sectors to minimize the number of providers who are completely out-of-stock.

We learned that compliance with the recommendation to conserve vaccine by deferring the fourth dose for healthy children depended on whether the provider had experienced a shortage. Fifty-eight percent of those who had experienced a shortage reported that they would defer the fourth dose for healthy children whereas only 29% of those who did not experience a shortage would defer the fourth dose for healthy children.

Although the intention was to provide flexible recommendations that address nearly every situation an immunization provider might encounter, some providers felt that the ACIP's recommendations, which varied with the patient's age, age at first PCV administration, number of doses of PCV already received, severity of shortage, and presence or absence of specified health conditions, were too complicated. Among 313 pediatricians reporting any barrier to the use of the ACIP's recommendations, 59% said that they had trouble remembering the recommendations and 57% said that they found the recommendations confusing.

When, in November of 2003, the manufacturer advised CDC that there might, once again, be shortfalls in PCV deliveries, the CDC and its partners adopted the following strategies for managing the shortage: 1. Work with the manufacturer to try to "even out" supplies of vaccine in both the public and private sectors, 2. Ask immunization providers to conserve vaccine by deferring the fourth dose for healthy children. Later, when the manufacturer reported more severe problems with vaccine delivery, the recommendation was extended to include the deferral of the third and fourth doses. 3. Make recommendations as simple as possible and make them in consultation with representatives of the American Academy of Family Physicians, the American Academy of Pediatrics, the ACIP and the FDA. 4. Encourage compliance with the recommendation to defer the third and fourth doses by providing information on the observed effectiveness of incomplete schedules.

The CDC's recommendations for coping with the current PCV shortage are simple: 1. Defer the third and fourth doses for healthy children. Another way of saying this is "Give no more than 2 valid doses to any healthy child until the

shortage is over." 2. Vaccinate "high risk" children as if there were no shortage. The "high risk" children are specified by the ACIP and AAP and are those who have chronic health conditions that impair their immunity to *S. pneumoniae* infections, put them at higher risk of a severe disease should they become infected with *S. pneumoniae,* or increase their susceptibility to invasive *S. pneumoniae* infections.

The list of children who should receive the full 4-dose series despite the shortage includes children with sickle cell disease and other hemoglobinopathies, anatomic asplenia, chronic diseases (e.g., chronic cardiac and pulmonary disease and diabetes), cerebrospinal fluid leak, human immunodeficiency virus infection and other immunocompromising conditions, immunosuppressive chemotherapy or long-term systemic corticosteroid use; children who have undergone solid organ transplantation, and children who either have received or will receive cochlear implants. All these children have been identified as being at either "high risk" or "presumed high risk" for severe invasive pneumoccocal disease.

The current recommendations for managing the shortage have two parts, one pertaining to healthy children and the other pertaining to high risk children. I will address the data supporting the use of an abbreviated, 2-dose schedule in healthy children first. There are just two sources of effectiveness data, a pre-licensure randomized, controlled trial and post-licensure observational data from the Active Bacterial Core Surveillance program.

In a large study of 37,868 children, 1 or 2 doses of pneumococcal conjugate vaccine were protective during the 2-month interval before the next dose with a point estimate of 86% efficacy but a 95% confidence interval that included zero.

Based on a preliminary, case-control analysis of data from the CDC's Active Bacterial Corps Surveillance (ABCs) program, the routinely recommended 4-dose series has been 97% effective against invasive disease caused by serotypes represented in the vaccine with a 95% confidence interval of 76% to 100%. The effectiveness in children who received 3 doses before age 1 year has been 87% with a confidence interval of 71% to 94%, and the effectiveness in children who received 2 doses has been 94% with a confidence interval of 84% to 98%. I should point out that although the point estimate for the effectiveness of 2 doses is slightly higher than the estimate for 3 doses, the confidence intervals overlap meaning that the there is no statistically significant difference.

The available date on the effectiveness of incomplete schedules have significant limitations. The pre-licensure study was large but there were so few cases of

invasive *S. pneumoniae* caused by vaccine serotypes that the confidence interval for the estimate of the effectiveness of 1 or 2 doses was wide and included zero. The ABCs provides preliminary data that have been analyzed using case control design and have the potential limitations inherent in observational studies. Neither source of data provides much information about the duration of protection beyond a few months. Despite all these limitations, I think we can say that the evidence strongly suggests that 2 doses of PCV will provide significant protection for infants against invasive pneumococcal disease.

Regarding the effectiveness of incomplete schedules in children with chronic health conditions, we have no data. In the absence of data, the CDC and its partners recommend that children identified as being at high risk of pneumococcal disease continue to receive the full, 4-dose PCV series.

And now for some good news. Despite the last shortage, the incidence of invasive S. pneumoniae infection has dropped dramatically in the United States since the PCV was introduced. This slide, courtesy of Cynthia Whitney of the National Center for Infectious Diseases, shows a fall in the incidence of invasive pneumococcal disease among 1-year-olds from over 200 per 100,000 in 1998 and 1999 to 35 per 100,000 in 2002 and a similar drop among children less than 1 year of age.

In conclusion, we have dealt with a PCV shortage before and learned from that experience. With the continued cooperation of immunization providers there is every reason to believe that we will manage this current PCV shortage with minimal adverse effects on American children.