

PneumoADIP comment on the publication of Alaska data on serotype replacement May 2007

The April 25, 2007, edition of JAMA contains an important article by Rosalyn Singleton and colleagues reporting the experience with a 7-valent pneumococcal conjugate vaccine in Alaska and particularly in the Alaska Native populations who have a high incidence of invasive pneumococcal disease. The authors report that the incidence of invasive pneumococcal disease due to serotypes not included in the 7-valent vaccine increased significantly among Alaska Natives following widespread use of the 7-valent vaccine, a phenomenon known as replacement disease.

Since 2000 when 7-valent vaccine was introduced into the US immunization schedule, a small amount of replacement disease has already been observed in the general US population. The degree of replacement disease in the general US population as well as non-native Alaska residents has been small relative to the reductions in vaccine type disease. Among Alaska Native children less than 2 years of age, the degree of replacement disease, especially with serotype 19A, has been more significant than that seen in the general US population and therefore overall vaccine impact has been reduced.

The report shows that the overall impact of the vaccination program remains beneficial, even after accounting for the increases in non-vaccine type disease. Rates of overall invasive pneumococcal disease in Alaska Native children less than age 2 years remain ~40% lower than the rates observed in the pre-vaccine period – this reduction amounts to the continued prevention of about 150 cases per 100,000 per year (see figure A).

The study's conclusions stress two important points. First, post-introduction surveillance for invasive pneumococcal disease is critical as a tool for monitoring vaccine impact and for understanding if there are special populations in which the vaccine may not be as beneficial as it has been in the general population. The findings also indicate that continued efforts to develop and license new vaccines that protect against a wider range of pneumococcal strains are needed.

The amount of replacement disease among the Alaska Natives is more than expected. American Indians of the US Southwest and Australian Aboriginals share many epidemiologic similarities with Alaska Natives. They have also been using 7-valent vaccine, and in the case of the American Indians in the US Southwest the vaccine has been used for 3 years longer than in Alaska, yet surveillance in this region reveals no significant increases in non-vaccine type disease following its introduction. In the general population of the United States,

7-valent vaccine use has been followed by increases in 19A invasive disease but these increases are smaller than those observed in Alaska Natives.

We don't know how much of the increase in non-vaccine type disease may be caused by factors other than vaccine use. Serotype 19A is often resistant to antibiotics, and continuous use of antibiotics has shown to promote antibiotic-resistant pneumococci in communities with high antibiotic use. A significant increase in disease caused by serotype 19A was recently reported in Korea and also in southern Israel, where pneumococcal conjugate vaccines are not yet widely used. The increasing proportions of antibiotic resistant strains within serotype 19A in the US, Korea and Israel (Dagan R. ESPID 2007) suggest that the increase of 19A is not solely caused by vaccination, but may be also related to patterns of antibiotic use in specific communities.

Serotype 19A has previously been associated with increases in non-vaccine type disease in the general population of the USA following introduction of 7-valent vaccine. It is important because serotype 19A is included in the 13-valent conjugate vaccine currently in development by Wyeth Pharmaceuticals, and because preliminary immunologic evidence suggests that the 19F conjugate in GSK's 10-valent vaccine might potentially provide partial protection against 19A disease. Licensure of this vaccine is expected between 2008 and 2010. This means that, even if introduction of 7-valent is followed 3-4 years later by an increase in 19A disease, there is the potential to respond to the increase with a next generation vaccine by the time that it occurs. Further in the future, vaccines based on "common proteins" might be able to provide another valuable tool for diminishing disease due to vaccines not contained in pneumococcal conjugate formulations.

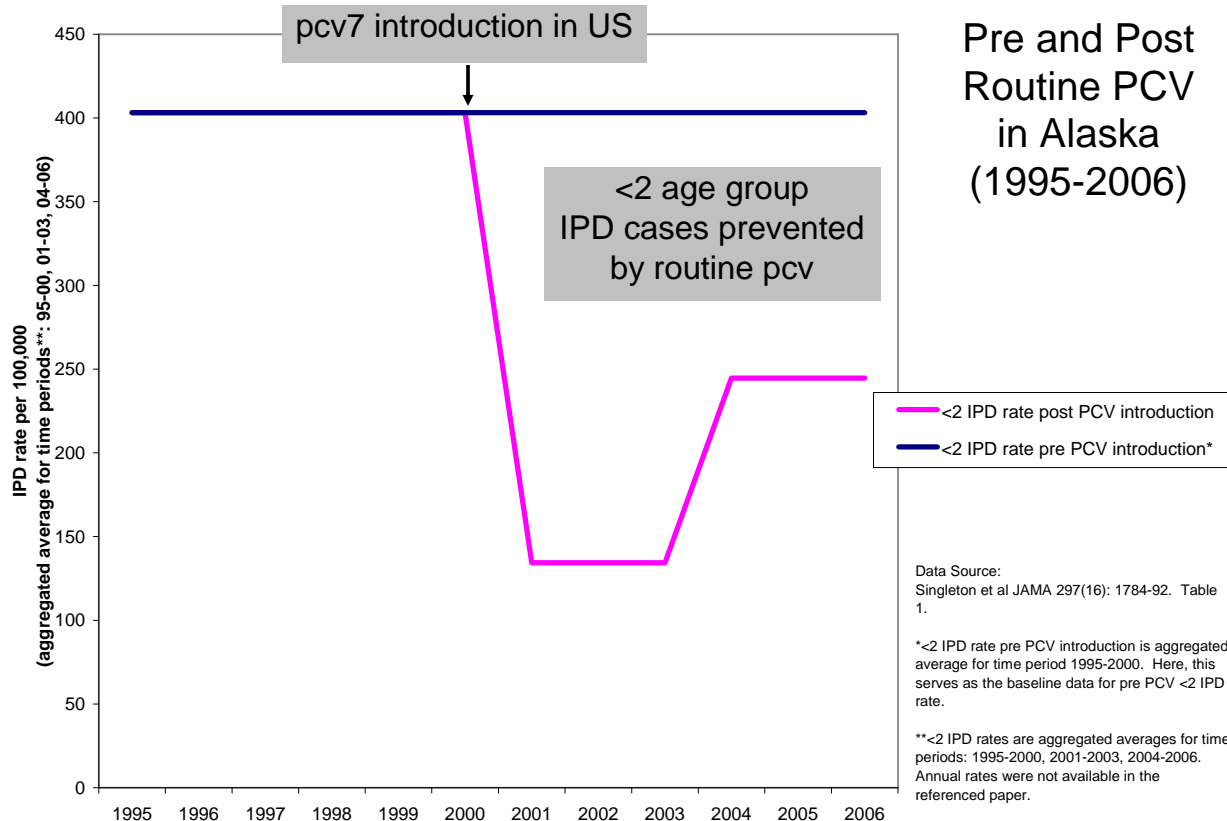
What is GAVI's PneumoADIP doing to understand serotype replacement and assure evidence-driven policies for vaccine introduction?

Working in collaboration with WHO and other partners, GAVI's PneumoADIP is taking steps to improve our understanding of the serotypes causing disease in developing countries and to support evidence-driven policies based on the best available data. PneumoADIP is currently working with WHO on a systematic review and meta-analysis of the published data on the global distribution of serotypes causing invasive pneumococcal disease in children worldwide.

To date, PneumoADIP, in collaboration with WHO, CDC, and others, has invested more than \$15M in strengthening surveillance for laboratory confirmed pneumococcal disease in more than 50 developing countries. PneumoADIP has also been awarded an additional \$19M over 4 years. This is to assure that there is a careful evaluation of the impact of 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in 2 early adopter countries in Africa.

Finally, PneumoADIP gathers strategic advice from international experts to provide guidance to GAVI and its partners on issues related to vaccine introduction.

Figure A. Pre and Post Routine PCV in Alaska Native Children <2 age group (1995-2006)



JAMA article citation:

Singleton RJ, Hennessy TW, Bulkow LR, et al "Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska Native children with high levels of 7-valent pneumococcal conjugate vaccine coverage" JAMA 297(16): 1784-92.

Other post-PCV introduction serotype replacement studies:

Flannery B, Hefferman RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med.* 2006; 144: 1-9.

Krause VL, Cook H, Selvey CE. Impact of 7vPCV and 23vPPV booster in eligible children in the Northern Territory of Australia: impressive, but not the total answer. In: Program and abstracts of the 5th Annual International Symposium on Pneumococcus and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract SY1.032006:55.

O'Brien KL, Shaw J, Weatherholtz R, et al. Epidemiology of invasive *Streptococcus pneumoniae* among Navajo children in the era before use of conjugate pneumococcal vaccines, 1989-1996. *Am J Epidemiol.* 2004; 160: 270-278.

O'Brien KL, Weatherholtz R, Millar EV, et al. Replacement invasive pneumococcal disease 9 years after introduction of PCV among a population at high risk for IPD: the Navajo Experience. In: Program and abstracts of the 5th Annual International Symposium on Pneumococcus and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract P04.17: 189.

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