# Invasive Pneumococcal Disease in Alaskan Children

## *Impact of the Seven-Valent Pneumococcal Conjugate Vaccine and the Role of Water Supply*

*Jay D. Wenger, MD,* Tammy Zulz, MPH,* Dana Bruden, MS,* Rosalyn Singleton, MD, MPH,* Michael G. Bruce, MD, MPH,* Lisa Bulkow, MS,* Debbie Parks, BS,* Karen Rudolph, PhD,* Debby Hurlburt, RN,* Troy Ritter, REHS, MPH,† Joseph Klejka, MD,‡ and Thomas Hennessy, MD, MPH**

**Background:** Alaska Native (AN) children, especially those in the Yukon-Kuskokwim region (YK-AN children), suffer some of the highest rates of invasive pneumococcal disease (IPD) in the world. Rates of IPD declined after statewide introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2001, but increased in subsequent years.

**Methods:** Population-based laboratory surveillance data (1986–2007) for invasive *Streptococcus pneumoniae* infection in Alaskan children <5 years old were used to evaluate the association of IPD rates and serotype distribution with immunization, socioeconomic status, and in-home water service.

**Results:** Introduction of PCV7 vaccine resulted in elimination of IPD caused by vaccine serotypes, but was followed by increasing rates of IPD caused by nonvaccine serotypes. Among YK-AN children IPD rates dropped by 60%, but then rose due to non-PCV7 serotypes to levels 5- to 10-fold higher than rates in non-YK-AN children and non-AN children. IPD rates in YK-AN children were twice as high in villages where <10% of houses had in-home piped water compared with villages where more than 80% of houses had in-home piped water (390 cases/100,000 vs. 146 cases/100,000, $P = 0.008$).

**Conclusions:** High IPD rates in Alaska are associated with lack of in-home piped water (controlling for household crowding and per capita income). The effect of in-home piped water is most likely mediated through reduced water supply leading to limitations on handwashing.

**Key Words:** invasive pneumococcal disease, water, pneumococcal conjugate vaccine, *Streptococcus pneumoniae*

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Nearly 50% of Alaskans live in the Anchorage metropolitan area, but one-third of the remaining population lives in small rural communities of 50 to 1000 persons dispersed throughout the remainder of the state. Alaska Native (AN) people comprise approximately 20% of the population and are the predominant inhabitants of small communities in the northern and western regions of the state.[1] These communities are not connected by a highway system, and many do not have piped water systems.

High rates of serious pneumococcal disease were recognized several decades ago in Alaska.[2] Rates of invasive pneumococcal disease (IPD) in AN children in the Yukon-Kuskokwim region in western Alaska (YK-AN children) are among the highest in the world.[3] Subsequent evaluations confirmed high rates of disease in other AN children, and identified a significant disparity in rates between AN children and non-AN children. For example, the rate of culture-positive pneumonia in AN children <2 years old was 10-fold higher than that of non-AN children <2 years old.[4]

Underlying diseases (eg, immunosuppressive disorders, congenital abnormalities, chronic lung disease, or prematurity) as well as behavioral risk factors (eg, day care attendance, household crowding, and lack of breast-feeding[5–7]) contribute to increased risk of IPD in children.[4,5,8–10] However, no combination of these previously identified risk factors explained a health disparity of the magnitude observed in Alaska, which was consigned to ". . . unexplored social, . . . and environmental factors."[4] Two recent studies from Alaska demonstrated that lack of in-home piped water (ie, hauling of water to and waste from the home) was associated with higher rates of hospitalization for respiratory diseases.[11,12]

Introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in early 2001 raised hopes of addressing IPD in Alaska populations, despite underlying causes. IPD caused by serotypes present in the vaccine decreased rapidly, narrowing the disparity between AN children and non-AN children but IPD rates caused by nonvaccine serotypes increased subsequently, specifically in AN children less than 5 years old.[13]

We evaluated IPD surveillance data from Alaska through 2007 to further characterize the impact of PCV7 vaccine introduction, and to evaluate potential associations between socioeconomic indicators, water supply, and IPD in the postvaccine era.

## METHODS

### Invasive Disease Surveillance

Since 1986, cases of IPD (defined as isolation of *S. pneumoniae* from a normally sterile site in an Alaska resident) are reported from clinical laboratories throughout Alaska to the CDC's Arctic Investigations Program (AIP) in Anchorage. Isolates are sent to AIP where identification, serotyping, and antimicrobial susceptibility testing are performed using standard methods. Annually, participating laboratories compare their records with a list of isolates received by AIP and report any missing cases.

Data on cases are collected from clinical laboratories, medical records, or the patient's clinician, and include demographic information, clinical syndrome and outcome. We report data on cases of IPD in children aged <5 years in Alaska identified between January 1, 1986 and December 31, 2007. We studied 3 specific time periods to assess impact of PCV7 and characterize disease in the conjugate vaccine era. Time periods were defined as:

- Period 1, prevaccine introduction (1996–2000).

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From the *Arctic Investigations Program, National Center for Preparedness, Detection and Control of Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska; †Division of Environmental Health and Engineering, Alaska Native Tribal Health Consortium, Anchorage, Alaska; and ‡Yukon-Kuskokwim Health Corporation, Bethel, Alaska.

Address for correspondence: Jay D. Wenger, MD, Arctic Investigations Program, Centers for Disease Control and Prevention, 4055 Tudor Centre Dr, Anchorage, AK 99508. E-mail: jdw2@cdc.gov.



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- Period 2, early vaccine period (2001–2004), during which rates in both AN children and non-AN children dropped below the lowest rates in period 1.
- Period 3, late vaccine period (2005–2007) during which rates in both AN children and non-AN children rose above period 2 nadirs.

### Socioeconomic Factors and Water Supply Data

The Rural Alaska Housing Sanitation Inventory documented in-home water service in rural areas of Alaska between 2001 and 2004. We obtained data on factors potentially associated with IPD (household size, income data, percent of homes heated with wood, and water service in villages/cities not in the inventory) at the village level from the 2000 US Census.[1] In-home water service was defined as pressurized water service within the household, either from a centralized piped water service system or a closed haul system. In a closed haul system, water is delivered to an external holding tank and distributed throughout the household in pressurized pipes. We calculated the percent of households with water service by AN health care system regions. In YK, we categorized villages (N = 55) into low service (<10% of households served), midlevel service (10%–<80% of households served), and high service (≥80% of households served).

### Vaccination Coverage

We obtained the coverage rate with 3 doses of PCV7 in 19- to 35-month-old children in the United States population overall, and for Alaskan children by race from the National Immunization Survey public use files for July 3, 2003 through June 3, 2007.[14] We obtained coverage data for AN children by region from computerized health records for AN children.

### Statistical Analysis

Vaccine coverage is presented with the 95% confidence interval for a binomial proportion. Statistical analyses and comparisons of rates and proportions between study periods were evaluated using the $\chi^2$ test (Mantel-Haenszel). *P*-values are exact where appropriate and 2-sided. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC), EpiInfo 3.5 (Centers for Disease Control, Atlanta, GA).

We used a multivariate analysis of variance model (MANOVA) to test if 3 potential risk factors (household size, per capita income, and water service level) jointly differed between YK and other regions. The unit of analysis was village/city. The city of Anchorage was presented separately for IPD rates and socioeconomic factors. It was not included in the MANOVA as it was the only unit of analysis in the region. We tested IPD rates among YK villages with different levels of water service by use of a trend test for Poisson rates.[15] We adjusted and tested for confounding of socioeconomic factors by the use of Poisson regression.

## RESULTS

### Vaccination Coverage

Among AN children, coverage with 3 doses of PCV7 in 19- to 35-month olds rose from 93% (95% CI: ±6.3%, July 2003–June 2004) to 98% (±3.6%, July 2006–June 2007).[14] Vaccine coverage in Alaska white nonhispanic children rose from 65% (±9%) to 90% (±5%) while coverage with 3 doses of PCV7 vaccine in the United States population rose from 71% (±1%) to 89% (±1%)[14] during the same time periods. Among YK-AN children, coverage rose from 95% to 98% during the same time periods (AN health system data).

### Overall IPD Rates in Alaskan Children

IPD rates in Alaskan children <5 years of age are shown in Figure 1. IPD in all Alaskan children declined from 97 cases/100,000 per year in the prevaccine period (period 1) to 41/100,000 in period 2 ($P < 0.002$), and then rose to 63/100,000 in period 3 ($P < 0.002$, period 2 vs. period 3). Rates of disease in AN children were 2- to 5-fold higher than in non-AN children during period 1. IPD rate disparities disappeared in 2001, when PCV7 was introduced, but re-emerged later, with rates in AN children 3 to 5 times higher than those in non-AN children ($P < 0.001$).

### IPD Rates by Ethnicity, Setting, and Vaccine Type Status

Table 1 shows rates of IPD, IPD caused by vaccine serotypes, and nonvaccine serotypes. Among AN children, rates of vaccine type disease were highest in YK. YK-AN children also had the highest rates of nonvaccine type disease before introduction of PCV7. Vaccine-type disease disappeared in all population groups. IPD due to nonvaccine serotypes increased in both AN children and non-AN children in recent years. Following an initial postintroduction decline in YK, rates of nonvaccine type IPD increased more than 3-fold ($P < 0.0001$, period 3 vs. period 2, Table 1). In all other population groups (except urban AN children) nonvaccine type IPD in period 3 also increased significantly ($P < 0.02$ for comparisons of period 1 vs. period 3).

### Serotype Distribution

Serotypes causing at least 90% of IPD in Alaskan children during each period are shaded in Table 2. In period 1, 11 serotypes caused 92% (201/219) of all IPD. In period 2, the most common 18 serotypes (causing 93% (71/76) of all IPD) included 8 of the 11 major serotypes in period 1 plus an additional 10 serotypes present previously, but which had not caused substantial amounts of disease. In period 3, three non-PCV7 serotypes (19A, 7F, and 6A), each among the 11 most common causes of IPD in period 1, caused 56% of all IPD. An additional 22% of all disease in period 3 was caused by serotypes that emerged as significant contributors to IPD in period 2. Serotypes included in the 13-valent pneumococcal conjugate vaccine under development caused 67% of IPD in period 3.

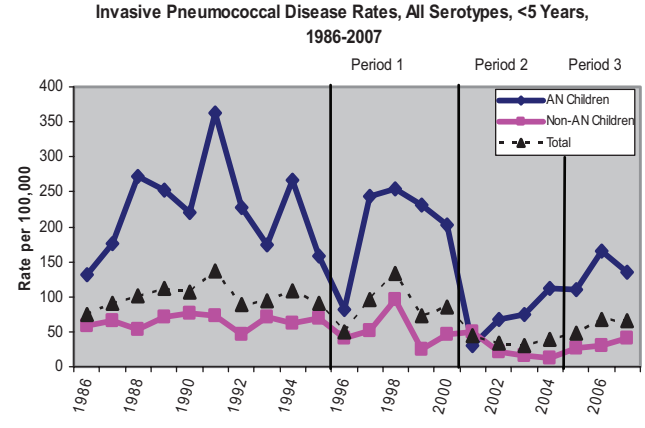


**FIGURE 1.** Invasive pneumococcal disease (IPD) in Alaskan children less than 5 years of age, 1986 to 2007, cases/100,000 children/y. Total rate (lines with triangles), rate in non-Alaskan Native children (lines with boxes) and rate in Alaskan Native children (lines with diamonds).

**TABLE 1.** Rates of Invasive Pneumococcal Disease (IPD) by Race, Geographic Location and Time Period, Alaskan Children <5 Year of Age

| | Period 1, 1996–2000 | Period 2, 2001–2004 | Period 3 2005–2007 | *P* Period 1 vs. 2 | *P* Period 2 vs. 3 |
|---|---|---|---|---|---|
| Rate of total IPD (cases of IPD/100,000 children <5) | | | | | |
| All | 97 (242)* | 41 (83) | 63 (101) | <0.001 | 0.003 |
| Alaska native–all | 227 (135) | 77 (42) | 142 (62) | <0.001 | 0.002 |
| YK | 547 (81) | 148 (18) | 426 (40) | <0.001 | <0.001 |
| Other rural | 87 (25) | 59 (16) | 87 (18) | 0.2 | 0.3 |
| Urban | 182 (29) | 53 (8) | 30 (4) | 0.001 | 0.3 |
| Alaska non-native–all | 56 (107) | 27 (41) | 32 (37) | <0.001 | 0.5 |
| Rural | 34 (18) | 26 (11) | 24 (8) | 0.5 | 0.9 |
| Urban | 65 (89) | 28 (30) | 34 (29) | <0.001 | 0.4 |
| Rate of IPD caused by serotypes in PCV7 (cases of PCV 7 serotype IPD/100,000 children <5)† | | | | | |
| Alaska native | | | | | |
| YK | 344 (51) | 8 (1) | 0 | <0.001 | 0.4 |
| Other rural | 70 (20) | 11 (3) | 10 (2) | <0.001 | 0.9 |
| Urban | 133 (18) | 0 | 0 | <0.001 | — |
| Alaska non-native | | | | | |
| Rural | 28 (15) | 7 (3) | 0 | 0.02 | 0.1 |
| Urban | 49 (67) | 11 (12) | 0 | <0.001 | <0.002 |
| Rates of IPD caused by serotypes not in PCV7 (cases of non PCV 7 serotype IPD/100,000 children <5)† | | | | | |
| Alaska native | | | | | |
| YK | 142 (21) | 124 (15) | 405 (38)‡ | 0.7 | <0.001 |
| Other rural | 14 (4) | 47 (13) | 77 (16)‡ | <0.02 | 0.2 |
| Urban | 38 (6) | 47 (7) | 30 (4) | 0.7 | 0.5 |
| Alaska non-native | | | | | |
| Rural | 5.7 (3) | 19 (8) | 24 (8)‡ | 0.06 | 0.6 |
| Urban | 10 (14) | 13 (14) | 34 (29)‡ | 0.5 | 0.002 |

*Number of cases in parentheses.
†Serotype specific rates represent cases in which serotype information is available.
‡Rate in period 3 significantly greater than rate in period 1, $P < 0.02$.

## Clinical Presentation

The proportion of AN children IPD case-patients with pneumonia rose from 62% (period 1) to 71% (period 3, $P > 0.05$). A higher proportion of YK case-patients had pneumonia (80%) than AN children from outside of YK (54%, $P < 0.01$). The proportion of non-AN children case-patients with pneumonia rose from 17% in period 1 to 30% in period 3 ($P = 0.05$). AN children case-patients were more likely to have pneumonia than non-AN children in each time period ($P < 0.01$), while non-YK AN children did not differ significantly from non-AN children. Seven to 15% of case-patients had meningitis, with no significant difference by race or time period. The case fatality rate ranged from 1.7% to 2.5%, with no significant difference by race or time period.

## Underlying Diseases

Information on underlying diseases was available for at least 94% of patients in periods 2 and 3, but only 39% of patients from period 1. Among those with information, 12%, 18%, and 38% reported underlying diseases in periods 1, 2, and 3, respectively ($P < 0.01$ for period 1 or 2 compared with period 3). During periods 2 and 3,YK-AN children were more likely to report an underlying illness (22% and 49% for period 2 and period 3, respectively) than non-YK-AN children (21% and 43%, respectively), or non-AN children (10% and 19%, respectively) though the differences between population groups within a time period are not statistically significant.

Asthma was a common underlying disease reported for YK-AN children (11% and 24% of YK-AN children in periods 2 and 3, respectively). In contrast, 8% and 4% of non-YK-AN children cases reported these diseases in period 2 and 3, respectively, and 2% and 8% of non-AN children cases reported asthma during the same time periods. The only other commonly reported underlying disease, congenital anomalies or abnormalities, was reported in 5% to 13% of each group in period 2 and 15% to 17% of each group in period 3. Thus, the increase in proportion of children with an underlying disease is likely attributable to both (1) a general increase in reporting underlying disease and (2) an increasing proportion of all cases occurring in YK-AN children (22% of cases in period 2 and 41% of cases in period 3), in whom asthma was more commonly reported in all periods.

## Geographic Variation in IPD Rates and Socioeconomic Risk Factors for IPD

IPD rates in the postvaccine era (periods 2 and 3 combined) varied widely among geographic regions in Alaska (Table 3). YK had significantly higher rates of IPD (267 cases/100,000 children <5) than the 3 next highest regions (67, 94, and 80/100,000, $P < 0.0001$), which in turn had higher rates of IPD than other regions (all <45/100,000, $P = 0.004$). YK had the lowest average annual per person family income and the highest number of average persons per household (Table 3). YK also had the smallest proportion of houses with piped, in-home water service (61%). YK differed significantly in water service level, household size, and per capita income from the other regions (MANOVA, $P < 0.01$).

Within YK communities identified as having low water service the rate of IPD was 391/100,000 children <5 years old; communities with midlevel water service had a rate of 263/100,000 and communities with high water service had a rate of 147/100,000 (*P*-for trend = 0.008, Table 4). The association between IPD rate and water service remained statistically significant when stratified by income per person, median family income, median household size, and proportion of houses heated with wood ($P < 0.02$ for each comparison, data not shown).

## DISCUSSION

IPD decreased in Alaska immediately after introduction of PCV7, but increased in subsequent years, especially in YK-AN

**TABLE 2.** Most Common *S. pneumoniae* Serotypes Causing Invasive Pneumococcal Disease (IPD) in Alaskan Children <5-Year-Old by Time Period

| Serotype | Period 1: 1996-2000 Cases, (%) | Period 2: 2001-2004 Cases, (%) | Period 3:2005-2007 Cases, (%) |
|---|---|---|---|
| 14* (PCV7) | 67 (31)‖ | 7 (9) | - |
| 6B* (PCV7) | 30 (14) | 4 (5) | - |
| 19F* (PCV7) | 27 (12) | 2 (3) | - |
| 18C * (PCV7) | 15 (7) | 2 (3) | - |
| 9V * (PCV7) | 12(6) | 1 (1) | 1 (1) |
| 23F * (PCV7) | 11 (5) | 3 (4) | 1 (1) |
| 19A* | 10 (5) | 18 (24) | 30 (31) |
| 4 * (PCV7) | 9 (4) | - | - |
| 6A* | 8 (4) | 4 (5) | 6 (6) |
| 1* | 7 (3) | - | - |
| 7F* | 5 (2) | 2 (3) | 20 (20) |
| 38 | † | 5 (7) | 1 (1) |
| 33F | 3 (1) | 4 (5) | 4 (4) |
| 15C | 1 (0.5) | 3 (4) | 1 (1) |
| 22F | 3 (1) | 3(4) | 4 (4) |
| 10A | † | 3 (4) | 2 (2) |
| 15B | 1 (0.5) | 3 (4) | 1 (1) |
| 12F | † | 2 (3) | 6 (6) |
| 3* | † | 2 (3) | 6 (6) |
| 8 | † | 2 (3) | - |
| 22A | 1 (0.5) | 2 (3) | 1 (1) |
| 23B | † | 1 (1) | 3 (3) |
| 15A | 1 (0.5) | - | 2 (2) |
| 16F | † | - | 2 (2) |
| 35F | 1 (0.5) | - | 2 (2) |
| 9N | 2 (1) | - | 2 (2) |
| 17F | § | 1(1) | 1 (1) |
| % of IPD (top 3 serotypes) | 58% | 41%¶ | 58%¶ |
| % of IPD (top 5 serotypes) | 71% | 51%¶ | 71%¶ |
| % of IPD (top 10 serotypes) | 92% | 73%¶ | 86%¶ |
| % of IPD (PCV7 serotypes) | 80% | 26%¶ | 2%¶ |
| % of IPD (6 additional serotypes in PCV13) | 13% | 35%¶ | 65%¶ |
| % of IPD (PCV13 serotypes) | 92% | 61%¶ | 67%¶ |

*In 13-valent pneumococcal conjugate vaccine.
†Isolated from IPD in Alaskan children <5 yr of age in 86–95.
‡No IPD, but present in carriage specimens from period 1 IPD.
§Isolated from Alaskan adults during period 1.
¶*P* value <0.05 when compared with previous period.
‖Shading shows rank-ordered serotypes included in cumulative frequency of ≥90%.

children. By 2007, IPD rates in YK-AN children were again 5 to 10 times higher than in other populations in Alaska. We characterized potential contributors to this persistent increased risk, and identified a significant association of IPD with lack of in-home water supply.

Among Alaska regions, YK has the lowest per capita income, the largest households and the lowest proportion of villages with a piped water supply. Within YK, lack of piped water was significantly associated with risk of IPD (controlling separately for per capita income, household crowding, and wood heating in the home). The most likely explanation for such an effect is that reduced availability of water decreases handwashing, leading to increased transmission of respiratory pathogens. A randomized trial of handwashing in Pakistan showed 50% lower rates of lower respiratory tract infection in the hand-washing group.[16] Reduction in risk of respiratory disease was associated with handwashing in a military population,[17] for SARS transmission,[18] and for respiratory infections in general.[19] For IPD, the implications of increased person-to-person transmission of respiratory pathogens may be 2-fold–(1) enhanced spread of pneumococcal colonization and (2) increased transmission of other respiratory viruses that could facilitate development of IPD among persons colonized with pneumococci. The impact of water supply on IPD appears to be unrelated to water purity or contamination. Neither study identifying water supply as a risk factor for increased rates of hospitalization for skin and respiratory infection in Alaska found an associated increase in diarrheal diseases.[11,12]

**TABLE 3.** Water Supply, Socioeconomic Data and Invasive Pneumococcal Disease (IPD) Rates (2001–2007) by Region Within Alaska

| Region | Total Population Size | Population (<5 Years of Age) | % of Population Alaska Native | No. Villages | Overall Rate of IPD <5 Years of Age (Cases) | Proportion of Households With Water Service | Socioeconomic Factors | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Median Persons/Household | Per Capita Income ($1000) | Median Family Income ($1000) |
| YK | 23,415 | 3024 | 88% | 50 | 267 (59) | 61% | 4.7 | 6.5 | 33.2 |
| A | 7965 | 900 | 86% | 13 | 94 (6) | 86% | 4.4 | 14.7 | 58.1 |
| B | 9196 | 1045 | 79% | 17 | 80 (6) | 72% | 3.8 | 9.8 | 40.9 |
| C | 7445 | 675 | 73% | 26 | 67 (3) | 89% | 3.4 | 17.0 | 57.4 |
| D | 6346 | 685 | 71% | 7 | 44 (2) | 100% | 3.9 | 17.4 | 68.2 |
| E | 259,889 | 21,069 | 10% | 1 | 37 (57) | 100% | 3.2 | 20.0 | 63.7 |
| F | 143,494 | 9693 | 12% | 124 | 37 (27) | 95% | 3.3 | 17.8 | 56.9 |
| G | 96,228 | 7970 | 14% | 66 | 29 (16) | 92% | 3.1 | 14.9 | 46.8 |
| H | 72,954 | 4743 | 22% | 43 | 25 (8) | 95% | 3.1 | 19.8 | 62.4 |

**TABLE 4.** Rates of Invasive Pneumococcal Disease (IPD) in Children <5 yr of Age in YK, 2001–2007 by Water Service Level and Socioeconomic Factors

| Socioeconomic Factor | Socioeconomic Level | IPD Rate (Cases/100,000 per Year) | Univariate *P* |
|---|---|---|---|
| Water service | <10%* | 390.9 | 0.008 |
| | 10%–80%* | 262.9 | |
| | 80%+* | 146.7 | |
| Income per person | <$6000 per year | 286.3 | 0.71 |
| | ≥$6000 | 256.6 | |
| Median family income | <$32,000 per year | 302.6 | 0.33 |
| | ≥$32,000 | 232.4 | |
| Household size | ≥5 persons | 345.0 | 0.06 |
| | <5 persons | 199.2 | |

*Of homes served with running water.

The retrospective, observational nature of our study limits our ability to conclusively define the role of water supply in IPD in Alaska. It is possible that the elevated risk we identified represents the impact of other factors associated with water supply. Data from other sources provides some information on the potential role of other putative risk factors. Several studies suggest a slightly higher prevalence of underlying illnesses associated with risk of IPD[6,7,10,20] among AN children, including major birth defect anomalies,[21] low birth weight,[22] and anemia.[23] In period 3, 49% of YK-AN children and 43% of non YK-AN children with IPD reported an underlying disease. While increased rates of children with underlying disease may contribute to increased overall IPD rates, even if all cases reporting underlying disease are removed from the analysis, rates of disease in YK-AN children was still 4-fold greater than the rate in non- YK-AN children. Thus, while presence of underlying diseases increases risk for IPD, they do not explain the increase in rates observed in YK-AN children.

Behavioral risk factors associated with IPD in children include day care attendance, household crowding, lack of breast-feeding, and possibly indoor air pollution, the most likely correlate of which in Alaska is use of wood for heating.[5–7,20,24] Some data is available to address their potential contribution to increased rates of disease in YK-AN children. There are 8 licensed day care facilities in the Southwest region of Alaska, which includes YK. In contrast, there are 5 times more daycare facilities per unit population elsewhere in Alaska.[25] Thus, licensed day care attendance is unlikely to be a major contributor to increased risk of IPD in YK-AN children. Most (76%) women in Southwest Alaska are breast-feeding their babies at 4 weeks postpartum, well within the range of all regions in Alaska (70%–86%), therefore, differential breast-feeding rates do not appear to contribute to the disparity in risk.[26] Finally, according to US Census data, the proportion of homes heated with wood was low in YKD, did not differ significantly among water service categories (range among water service categories, 8.9%–10.5%) and thus did not contribute to the increased risk attributed to lack of in-home water supply. We addressed household crowding and income level directly in the analysis (Results section, and Table 4) and demonstrated that the association of IPD with water supply was independent of these risk factors. Additional study is needed to confirm this association since it is possible that other unidentified covariates may contribute to the apparently increased risk associated with lack of in-home water use. A prospective evaluation of the impact of provision of in-home piped water on infectious diseases in AN people is now underway.

The interaction of several factors led to multiple levels of risk in Alaska (Table 1). In all groups, from YK-AN children (highest risk) to non-AN rural children (lowest risk), introduction of PCV7 was accompanied by rapid disappearance of vaccine-type IPD. In 4 of 5 population groups, disappearance of PCV7 strains was followed by statistically significant increases in rates of disease caused by nonvaccine strains. As a result, the net impact of PCV7 in Alaskan children (where 80% of baseline disease was caused by vaccine type strains) was a 30% decline in IPD. This finding contrasts with the experience in the general US population, where overall disease rates in children <5 years of age fell from 99 to 23 cases/100,000 between 1998 to 1999 and 2004 (a 77% decrease) and rates of nonvaccine type IPD rose minimally.[27] Rates of IPD in White Mountain Apache children less than 2 years old in Arizona decreased from 470 to 120/100,000 after PCV7 introduction, with no increase in nonvaccine type IPD.[28] In Spain and France, countries with substantially lower PCV7 coverage rates, a modest overall reduction in rates of vaccine type IPD (21% and 40% decrease in children <2, respectively), was associated with a marked increase in nonvaccine type IPD rates (85% and 530%, respectively).[29,30] However, both studies noted an overall increase in IPD rates in the postvaccine era, and the impact of concurrent changes in surveillance methodology was unclear.[31] While long-term follow-up from a vaccine efficacy trial in South Africa suggests an increase in nonvaccine serotype IPD, data from other developing countries with population-wide use of PCV7 is not yet available.[32]

Several factors may contribute to the differences observed in nonvaccine serotype IPD in the postvaccine era. High rates of IPD in AN children are propelled by intense transmission of the pathogen and possibly viral cofactors, by household crowding, lack of piped water supply, and other unidentified factors. IPD after PCV7 introduction is likely a function of (1) level and duration of coverage with PCV7, (2) underlying transmission characteristics operating in the population of concern, (3) host characteristics, and (4) invasiveness of existent serotypes.[33] The complex interplay between these and other factors is illustrated by varying patterns of replacement noted in Alaska, the rest of the United States, and western Europe.

Our findings on incidence and serotype distribution are limited by the small population size leading to small numbers of cases and increased variability of the point estimates. Long-term surveillance is important to confirm the trends we identified. It is also possible that variations in surveillance sensitivity exist. However, increased sensitivity would only lead to even more elevated rates of IPD, emphasizing the importance of addressing key risk factors. In addition, the association of IPD with water supply was noted not only across regions (where some variation in surveillance capacity is possible), but also within the highest risk region (where surveillance is uniform), suggesting it is not a surveillance artifact. While IPD rates were available each year, data on crowding and income were projected from the 2000 census, and though changes in these parameters could have occurred over the course of the study, it is unlikely that these parameters changed substantially. Finally, the association between water service and IPD rates was demonstrated at the village level, and may not represent the strength of the association at the individual or household level.

High rates of IPD in Alaska are associated with lack of in-home piped water, an effect most likely mediated through limitations on handwashing. The pattern of emergence of serotypes after vaccine introduction highlights the potential of broader spectrum pneumococcal vaccines and the importance of continued surveillance, especially in developing countries where environmental conditions predispose to high risk of IPD. While develop-

ment of vaccines with broader coverage will undoubtedly reduce IPD burden, addressing infrastructure disparities such as in-home water supply may be a key component for controlling IPD in Alaska and other areas where such risk factors for IPD exist.

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