Contributions of Native Americans to the global control of infectious diseases

Mathuram Santosham [a,*], Raymond Reid [a], Aruna Chandran [a], Eugene V. Millar [a],
James P. Watt [a], Robert Weatherholtz [a], Connie Donaldson [a], Janné Croll [a],
Lawrence H. Moulton [a], Claudette M. Thompson [b],
George R. Siber [c], Katherine L. O'Brien [a]

[a] *Center for American Indian Health, Department of International Health, Johns Hopkins University,
621 N. Washington Street, Baltimore, MD 21205, United States*
[b] *Department of Epidemiology, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, United States*
[c] *Wyeth Vaccines, 401 North Middletown Road, BH 21101, Pearl River, NY 10965, United States*

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Abstract

For over a half of a century, Native American populations have participated in numerous studies regarding the epidemiology, prevention and treatment of infectious diseases. These studies have resulted in measures to prevent morbidity and mortality from many infectious diseases. The lessons learned from these studies and their resultant prevention or treatment interventions have been applied around the world, and have had a major impact in the reduction of global childhood morbidity and mortality.
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Key messages

In the keynote address (The Robert Austrian Lecture) for the 5th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-5) in Alice Springs, Australia, I highlighted the numerous contributions Native American populations have made to the control and prevention of infectious diseases worldwide. The participation of countless American Indian and Alaska Native individuals, families and communities in biomedical research over the last 3 decades has helped to identify the major causes of death and disability in these very communities and to determine effective strategies for disease treatment and prevention. Tremendous gains in child survival and general health status of Native Americans have been made as a result. Moreover, much of the knowledge gained from these studies has been applied in many populations around the world and has met with great success. This paper reviews the major achievements in Native American health that have been made to date. Without the dedicated efforts of study personnel and the participation of generations of Native Americans, this work and these successes would not have been possible.

Mathuram Santosham

Department of International Health and Department of Pediatrics, Johns Hopkins University

1. Introduction

There are more than 500 American Indian and Alaska Native (AI/AN) federally recognised tribes in the United States (US). These tribes have a rich diversity of ethnic and cultural heritage. In 2004, an estimated 4.4 million people in the US identified themselves as AI/AN alone or in combination with other ethnic groups [1]. Prior to the arrival of Europeans, diseases such as smallpox, measles, varicella,

* Corresponding author. Tel.: +1 410 955 3952/6931;
fax: +1 410 614 1419/955 2010.
E-mail address: msantosh@jhsph.edu (M. Santosham).

cholera, diphtheria, plague, pertussis, and malaria had not been described in the New World [2]. Following the migration and settlement of Europeans, several epidemics of infectious diseases occurred, and Native Americans succumbed to these diseases at remarkably high rates. To this day, rates of morbidity and mortality from some infectious diseases are disproportionately high among AI/AN populations [3], and a persistent gap in overall health status remains between AI/AN and non-Hispanic Whites in the US [4].

Over the last century, the participation of AI/AN populations in a variety of research efforts has helped to establish the health priorities of AI/AN communities, to evaluate the effectiveness of medical interventions, and, most importantly, to achieve significant reductions in infectious disease morbidity and mortality in these populations. Moreover, the dissemination of knowledge from these studies has also led to improved prevention and control of infectious diseases in many other populations around the world. In this review, we describe the contributions of Native Americans to infectious disease research and highlight the major improvements in health status in these populations, placing special emphasis on the Navajo and White Mountain Apache tribes in the southwestern US.

1.1. Trachoma

Trachoma is the leading preventable cause of blindness worldwide. Trachoma is a chronic follicular conjunctivitis caused by the bacterium *Chlamydia trachomatis*. Repeated infections result in scarring of the conjunctiva and cornea, which ultimately can lead to corneal opacification and blindness [5]. *C. trachomatis* is transmitted via ocular and respiratory secretions, and by insect vectors such as house flies [5]. Once common around the world, improvements in water quality and sanitation have virtually eliminated trachoma from the developed world. Nevertheless, the World Health Organization (WHO) estimates that trachoma is responsible for approximately 1.3 million cases of blindness annually, almost exclusively in the developing world. Trachoma is endemic in 55 countries; the prevalence of active disease in children 1–9 years of age is as high as 30% in some districts in Africa, Asia, and the Eastern Mediterranean [6].

In the early part of the 20th century, exceedingly high rates of trachoma among AI/AN populations were considered a "veritable scourge among the Indians" [7]. According to the Public Health Service, the prevalence among tribes across the US was 23%, and likely attributable to the poor living conditions on Indian reservations where household crowding and lack of sanitation were common [8]. In 1937, the curative effects of oral sulfanilamide antibiotics for trachoma were reported among 140 patients at Rosebud Indian Hospital in Rosebud, South Dakota [9]. Subsequent controlled trials among AI children from the southwestern US (including Navajo, Apache, Paiute, and Pima tribal members) attending the Stewart School in Carson City, Nevada demonstrated

the clear benefit of sulfa antibiotics for the treatment of trachoma [10], a treatment that is still widely used today for the prevention of blindness worldwide.

1.2. Hepatitis B

Chronic infection with hepatitis B virus (HBV) is a major cause of cirrhosis and liver failure, and is a risk factor for the development of hepatocellular carcinoma (HCC). In the pre-vaccine era, 5–29% of Alaska Natives (ANs) had serologic evidence of HBV infection (i.e. seropositivity for HBV) [11]. A recent study among Canadian Inuit reported HBV-seropositivity rates of 5%, 20 times higher than non-native Canadians [12]. Prior to routine use of hepatitis B vaccine, the risk of HCC among ANs chronically infected with HBV was 148-fold higher than their non-infected counterparts [13].

In 1981, the safety and efficacy trial of a plasma-derived hepatitis B vaccine was conducted among Alaskan Yupik Eskimos [14]. The vaccine afforded significant protection against hepatitis B disease; the incidence of hepatitis B infection decreased from 50 per 1000 before vaccination to 19 per 1000 after vaccination ($p < 0.002$). Follow-up studies in the early 1990s demonstrated continued immunogenicity and protection against clinical disease; in the 1630 individuals who received at least one dose of vaccine, none were persistently positive for hepatitis B surface antigen or developed evidence of clinical disease in the subsequent 10 years [15]. In 1982, a plasma-derived hepatitis B vaccine became available in the US for high risk populations. Following the development of recombinant hepatitis B vaccines, routine immunisation was recommended for all infants in 1991 [16]. Similar vaccination programs for the prevention of HBV infection have now been adopted in many countries around the world.

1.3. Tuberculosis

Though rates of tuberculosis (TB) among AI/AN populations have declined considerably in the last decade, TB continues to be an important problem among AI/AN populations. According to the National Center for Health Statistics, in 2002, the age-adjusted incidence rate of TB among AI/AN populations was twice the rate among the general US population, and seven times the rate among non-Hispanic Whites. The relative decline in the incidence of TB has been substantially smaller among AI/AN populations than among other groups in the US; from 1993 to 2002, TB case rates decreased by 58.3% among non-Hispanic Whites, by 49.7% among Hispanics, and by 39.6% among AI/AN populations [17]. The reasons for this slower decline are not known, but may be related to access to health care, missed opportunities for screening, and lower socioeconomic status [18].

The current TB vaccine, Bacille Calmette-Guérin (BCG), is an attenuated strain of the organism *Mycobacterium bovis*.

Table 1
Duration of diarrhoea and weight gain for children receiving four different ORS solutions

	Group A[a]	Group B[b]	Group C[c]	Group D[d]
Duration of diarrhoea (days)	1.9 ± 0.0	1.8 ± 0.2	2.0 ± 0.2	1.9 ± 0.2
%Weight gain at end of illness	1.4 ± 0.4	1.1 ± 0.5	−0.1 ± 0.4	0.9 ± 0.4

Data from: Santosham et al. [26].
ORS composition in each group:
[a] Group A (mmol/L): Na 90, K 20, chloride 80, bicarbonate 30, osmolality 333; glucose 20 g/L.
[b] Group B (mmol/L): Na 50, K 20, chloride 50, bicarbonate 0, osmolality 251; glucose 20 g/L.
[c] Group C (mmol/L): Na 30, K 20, chloride 30, bicarbonate 0, osmolality 211; glucose 20 g/L.
[d] Group D (mmol/L): Na 30, K 20, chloride 30, bicarbonate 0, osmolality 388; glucose 50 g/L.

In the 1930s, the first randomised placebo controlled trial of BCG was conducted among >3000 AI individuals aged 1 month to 20 years from a number of tribes [19]. During the subsequent 3 years, a 10-fold reduction in cases of tuberculosis was observed among vaccinees compared with unvaccinated controls. Recently, a 60-year follow-up study of the original study population demonstrated a vaccine efficacy of 52% against culture-confirmed pulmonary TB, and 63% against extrapulmonary TB [20]. Today, BCG is widely used around the world, particularly in regions where regular screening for TB is not possible.

1.4. Diarrhoeal disease and dehydration

Diarrhoea is a leading cause of morbidity and mortality among children in developing countries. In the US, diarrhoea results in approximately 1.5 million outpatient visits, 200,000 hospitalisations, and 300 deaths per year [21]. In the late 1970s and early 1980s, extremely high rates of diarrhoea were documented in the White Mountain Apache Tribe. Among children 4–12 months of age, diarrhoeal attack rates were as high as 6–8 episodes per child per year [22].

Oral rehydration solution (ORS) is a well-established form of therapy for the treatment of diarrhoeal dehydration. ORS was first introduced in the 1940s by Harrison, and was shown to prevent dehydration in outpatients with diarrhoea in the US [23]. Subsequently, a similar solution was commercially produced and distributed in powder form throughout the US. This solution contained 50 mmol/L of sodium and 8% carbohydrates [24]. However, in the 1950s, cases of hypernatraemia, some resulting in death, were reported among children treated with this form of ORS in the US [25]. Several factors may have contributed to the development of hypernatraemia, including the aggravation of diarrhoea due to the high carbohydrate content of the ORS and incorrect reconstitution of ORS by caretakers due to poor instructions [24]. Because of these cases of hypernatraemia, most paediatricians in the US stopped using ORS as a standard form of management of acute diarrhoea. In the 1960s, following physiologic studies showing coupled sodium-glucose absorption in the small intestine, a new ORS formulation was developed and recommended by WHO. This solution contained (mmol/L): sodium 90, chloride 80, bicarbonate 30, potassium 20; and glucose 20 g/L [24]. This solution was shown

to be safe and efficacious for the treatment of dehydration secondary to diarrhoea among children and adults of all ages in developing countries.

Paediatricians in the US continued to be resistant to the use of ORS due to past experiences with hypernatraemia and to the relatively sparse data available on the use of ORS in developed countries. From 1981 to 1983, a double-blind multi-center study comparing four different ORS solutions containing different concentrations of sodium, glucose, and bicarbonate was conducted. One of the study sites was the US Indian Health Service Hospital in Whiteriver, Arizona, serving the White Mountain Apache tribe [26]. Out of 140 children with diarrhoea, 137 (98%) were treated successfully with ORS in the outpatient setting, with no therapy-related complications. Table 1 shows the duration of diarrhoea and weight gain among patients randomised to various ORS formulations.

Infants in developing countries have been shown to experience 4–7 episodes of diarrhoea per year [27]. Because of traditional beliefs, food is often withheld by parents during a diarrhoeal illness; prior to the mid-1980s, this practice of withholding food during a diarrhoeal episode also was endorsed by physicians in both developed and developing countries. This practice resulted in aggravating the diarrhoea-malnutrition cycle [28]. One of the first studies showing the efficacy and safety of early feeding of hospitalised patients with diarrhoea was conducted among White Mountain Apache infants. Eighty-seven infants under 12 months of age being treated with ORS were randomised to receive a soy-based lactose free formula 4 h after hospital admission or to have food withheld for 48 h [29]. Overall, the group given early feeding had a shorter duration of diarrhoea and less mean stool output (Table 2). These findings were used by the WHO to promote early feeding for children with diarrhoeal illnesses around the world, and the contributions of the White Mountain Apache tribe to this work were

Table 2
Stool output and duration of diarrhoea in White Mountain Apache children receiving early feeding vs. withholding feeding

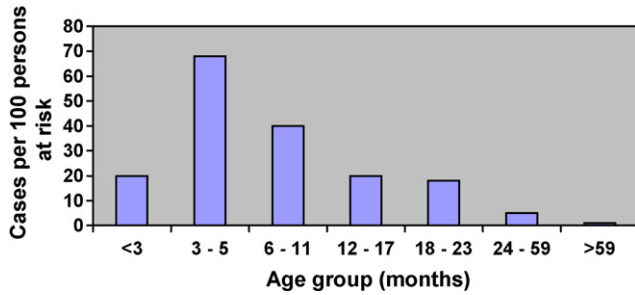|	Early feeding	Feeding withheld	p-Value
Total stool output (mL/kg)	121 ± 129	299 ± 319	0.001
Duration of diarrhoea (h)	54 ± 28	93 ± 56	<0.001

Data from: Santosham et al. [29].

Fig. 1. Incidence of rotavirus diarrhoea by age group on the White Mountain Apache Reservation from October to December 1981. Data from: Santosham et al. [32].

officially recognised by national and international organisations in 1995 [30].

1.5. Rotavirus

Worldwide, diarrhoea due to rotavirus (RV) is estimated to result in approximately 700,000 deaths per year, and children from the poorest countries account for the majority of these deaths [31]. RV was also an important pathogen in AI/AN communities. The age stratified attack rates of RV on the White Mountain Apache reservation during an RV epidemic in 1981 are shown in Fig. 1 [32].

From September 1985 to February 1987, two candidate RV vaccines were tested among 332 Navajo infants aged 2–5 months. One vaccine was a rhesus RV vaccine (RRV) and the other was a bovine RV vaccine (RIT 4237). There were 11 episodes of RV diarrhoea in the RRV group, 11 in the RIT 4237 group, and 9 in the placebo group; neither vaccine was found to be efficacious in protecting infants from RV diarrhoea [33]. Subsequently, from January 1992 to January 1994, a tetravalent reassortant rhesus RV vaccine (RRV-TV) was tested among 1185 Navajo, Gila River, White Mountain Apache, and San Carlos Apache infants aged 6–24 weeks [34]. This vaccine contained antigens from RV serotypes G1, G2, G3, and G4. Table 3 shows the vaccine efficacy and incidence of RV gastroenteritis overall and for serotypes G1 and G3. Overall efficacy in preventing RV gastroenteritis was 50%. Based on this and another multi-center trial [35], this vaccine was licensed in the United States, but was subsequently withdrawn due to concerns about its association with intussusception [36].

From 2001 to 2004, a live pentavalent RV vaccine containing five human-bovine reassortant RV isolates with human serotypes G1, G2, G3, G4, and P[8] was tested in a large multi-center trial. Children from the Navajo and White Mountain Apache tribes participated in this trial; this portion of the trial was independently powered to demonstrate efficacy. The vaccine was found to be 74% efficacious (95% confidence interval [CI]: 66.8%, 79.9%) against all RV disease and 98% efficacious (95% CI: 88.3%, 100%) against severe RV disease in the multi-center study population [37]; the results among Navajo and White Mountain Apaches are very similar to those found in the larger study population. This vaccine has recently been licensed (Rotateq®, Merck & Co., Inc., Whitehouse Station, NJ).

1.6. Haemophilus influenzae type b (Hib)

Prior to the routine use of Hib conjugate vaccines in infants, Hib was a leading cause of severe childhood illnesses including meningitis, bacteremia, cellulitis, and epiglottitis. Some of the highest documented rates of Hib disease were reported from AI/AN populations in the 1980s [38–40]. Among the White Mountain Apache, the average annual rate of Hib meningitis was 254 per 100,000 children <5 years of age, eight times higher than that of the general US population [41]. Among Navajo children <5 years of age, the incidence was 214 per 100,000 [39], while rates among Alaskan Eskimos were 491 per 100,000 children <5 years of age [40]. In addition, cases of invasive Hib disease among AI/AN children occurred at a younger age than in the general US population, with 30–50% of AI/AN cases occurring by 6 months of age and 80–90% of cases occurring by 1 year of age [39–41], compared with 20% and 60%, respectively, among the general US population [42,43].

Hib is encapsulated with a polysaccharide capsule (PRP), which serves as a major virulence factor for the organism. The first available Hib vaccine was based on the purified Hib capsular polysaccharide. In a large scale trial in Finland, the Hib-PRP vaccine was shown to be efficacious against invasive Hib disease when administered to children 18 months to 5 years of age, but not among younger children [44]. A study among White Mountain Apache children 24 months of age showed a 10-fold lower immune response to this vaccine compared with non-Hispanic Whites of the same age group [45].

In the absence of an effective active immunisation strategy for Hib among children younger than 18 months of age – the age group at highest risk – an alternative approach using passive immunisation with hyperimmune globulin containing high concentrations of Hib anti-PRP antibodies was considered. Bacterial polysaccharide immunoglobulin (BPIG) was prepared as a hyperimmune globulin from the plasma of adult volunteers immunised with Hib, meningococcal A and C, and pneumococcal polysaccharide vaccines. The efficacy of BPIG to prevent serious bacterial infections from Hib was evaluated among White Mountain and San Carlos Apache infants in a double-blind, placebo controlled trial in the early 1980s [46]. The administration of BPIG at 2, 6,

Table 3
Vaccine efficacy of RRV-TV against all-serotype rotavirus gastroenteritis, G1 and G3 disease, and severe disease

Disease description	%Efficacy (95% confidence interval)
All serotypes	50% (26–67)
Serotype G1	59% (−149 to 96)
Serotype G3	53% (25–72)
Severe disease	69% (29–88)

Data from: Santosham et al. [34].

and 10 months of age conferred significant protection against invasive Hib disease during the first 3 months after vaccination. There were seven cases of Hib in the placebo group and none in the BPIG group ($p = 0.007$) [46]. Additional studies of BPIG among Apache Indians were conducted between June 1986 and February 1989 that evaluated the efficacy of BPIG against invasive pneumococcal diseases, clinically diagnosed otitis media (OM), and X-ray confirmed pneumonia. There were 935 episodes of OM among BPIG recipients and 1167 episodes in the placebo group ($p < 0.001$) during the first 3 months after vaccination [authors' unpublished data]. The administration of BPIG also resulted in a significant reduction in X-ray confirmed pneumonia; there were 83 episodes in the BPIG group, compared to 155 in the placebo group ($p < 0.05$). There were four cases of invasive pneumococcal disease in the BPIG group versus 16 in the placebo group ($p < 0.01$; efficacy 75%, 95% CI: 26%, 92%). Even though the protective effects of BPIG on bacterial invasive diseases were clearly demonstrated, the high cost of production and the necessity for frequent large volume injections precluded its wide-scale use.

Conjugating a protein carrier to a polysaccharide antigen was shown to be an effective method for inducing immunity to the polysaccharide antigen in children less than 2 years of age, and eliciting a T-cell dependent immune response characterised by a booster response to repeated doses of vaccine and avidity maturation [47]. The introduction and widespread use of conjugate vaccines have played a major role in the prevention of life-threatening pediatric bacterial infections among children around the world. American Indian children played an important role in the field evaluation of Hib polysaccharide-protein conjugate vaccines in the 1980s. One of the first conjugate vaccines developed, PRP-OMP (PedvaxHIB®, Merck & Co., Inc., West Point, PA), uses an outer membrane protein complex of *Neisseria meningitidis* linked to Hib polysaccharide. The immunogenicity of PRP-OMP was evaluated among Navajo and White Mountain Apache children in the late 1980s [48]. In that study, approximately 70% of children 6–8 weeks of age achieved protective levels of Hib antibody ($>1\,\mu g/mL$) after a single dose administered at 2 months of age. This finding was particularly important in this population where many cases occurred in the first 6 months of life [48].

The efficacy of PRP-OMP was later evaluated among Navajo and Hopi children from 1988 to 1990 [49]. Over 5000 children were randomised to receive either two doses of PRP-OMP or placebo, beginning at 6 weeks of age. In children <15 months of age who had received two doses, vaccine efficacy was found to be 100% (Table 4). Based on the results from this trial, PRP-OMP was licensed for use in December 1990. Hib conjugate vaccines are now used widely around the world.

Post-licensure studies of Hib conjugate vaccines demonstrated a reduction in Hib colonisation in the oropharynx among vaccinated children [50]. Reductions in Hib carriage and transmission have resulted in a herd immunity effect in vaccinated communities; with the reduced transmission of Hib within a community, unimmunised individuals are also protected due to reduced exposure to the organism [51]. A study among Navajo children demonstrated that 30% immunisation coverage of children <2 years of age resulted in a 50% decline in disease incidence. In areas where 50% of children were immunised, a 70% reduction in invasive Hib disease was observed [52].

Since the introduction of Hib conjugate vaccine, rates of Hib carriage and disease among the Navajo and White Mountain Apache have declined dramatically [53]. There is concern that other serotypes not contained in the vaccines might emerge as important causes of disease (termed "serotype replacement") [54]. Theoretically, the decrease in Hib carriage rates could open an ecological niche in the human pharynx resulting in increased rates of carriage and disease due to other *H. influenzae* serotypes. Using active surveillance data, the incidence of *H. influenzae* type a (Hia) disease in the Hib vaccine era was evaluated among Navajo and White Mountain Apache populations [55]. This study documented high rates of invasive Hia disease (20 per 100,000 population <5 years of age) in these populations compared with that observed in the general US population, but no increase in Hia disease incidence following introduction of Hib vaccine. Population-based laboratory surveillance for invasive *H. influenzae* and other invasive bacterial pathogens has been essential to monitor the population based effects of routine childhood immunisation strategies against these pathogens and to monitor the effectiveness of disease prevention efforts.

Table 4
Efficacy of PRP-OMP Hib conjugate vaccine in Navajo and Hopi infants against Hib invasive disease

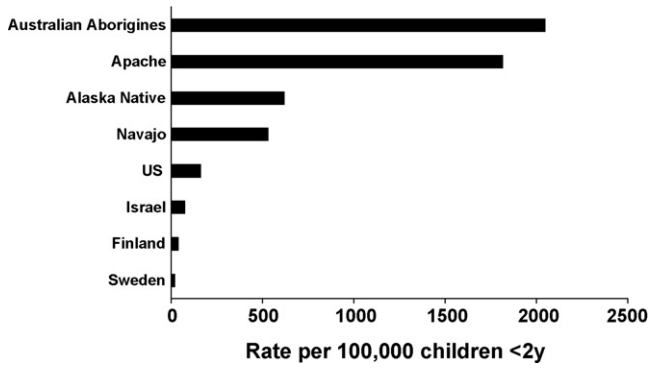|	Hib disease cases		*p*-Value	Vaccine efficacy
	Vaccine group	Placebo group		
At least one dose				
Disease onset <15 m	0/2588	21/2602	<0.001	100% (81–100)
Disease onset before 2nd dose	0/2588	8/2602	0.005	100% (41–100)
Two doses				
Disease onset <15 m	0/2056	13/2105	<0.001	100% (67–100)

Data from: Santosham et al. [49].

Fig. 2. Comparative rates of invasive pneumococcal disease worldwide. Data from: Aborigines: Torzillo et al. [61]; Apache: Cortese et al. [57]; Navajo: O'Brien et al. [62]; Alaska Native: Davidson et al. [58]; US: Robinson et al. [60]; Israel: Fraser et al. [63]; Finland: Eskola et al. [59]; Sweden: Burman et al. [56].

1.7. Streptococcus pneumoniae

AI/AN children have suffered from high rates of invasive pneumococcal disease (IPD) (Fig. 2) [56–63]. From 1983 to 1990, the average annual rates of IPD among White Mountain Apache and Navajo children <2 years were 1820 and 537 per 100,000 population respectively, 4–10 times higher than that of the general US population [57]. In 1996, just prior to the initiation of an efficacy trial of pneumococcal conjugate vaccine among the Navajo and White Mountain Apache, disease rates among the Navajo had declined to 307 per 100,000 population [62]. The decline of IPD may be related to a number of factors, including secular trends, improvements in overall health and living conditions, increased use of oral antibiotics for childhood illnesses, or a decrease in blood culturing practices [62,64].

The recent development and licensure of pneumococcal conjugate vaccines for infants and young children marks a major milestone in the history of preventing invasive pneumococcal infections, a leading cause of morbidity and mortality among children and adults worldwide. The efficacy of a 7-valent pneumococcal conjugate vaccine (PnCRM7; Wyeth Pharmaceuticals Inc., Philadelphia, PA) was evaluated in two pediatric populations in the US, one among a population in Northern California representative of the general US population [65], and another among American Indian children in the southwestern US [66]. From April 1997 to May 2000, 8292 Navajo and White Mountain Apache children were enrolled in a group-randomised trial of PnCRM7 vaccine. To assess the herd immunity effects of PnCRM7 vaccine during the trial, communities rather than individuals were randomised to receive either PnCRM7 or the control vaccine (a group C meningococcal conjugate vaccine, MnCC; Wyeth Pharmaceuticals Inc.). In the per protocol analysis of the primary efficacy group (children who were enrolled prior to 7 months of age), vaccine efficacy was 76.8% (Table 5). Analyses of the indirect effects of PnCRM7 on clinically diagnosed otitis media, radiologically confirmed pneumonia, and nasopha-

Table 5
Frequency of invasive disease and PnCRM7 vaccine efficacy by analysis group

	PnCRM7 cases	MnCC cases	PnCRM7 efficacy (95% CI)
Per protocol			
<7 months, VT	2	8	76.8% (−9.4 to 95.1)
<24 months, VT	2	10	81.7% (16.3–96.0)
Intention to treat			
<7 months, VT	2	11	82.6% (21.4–96.1)
<24 months, VT	2	14	86.4% (40.3–96.9)

VT: vaccine type (4, 6B, 9V, 14, 18C, 19F, and 23F). Data from: O'Brien et al. [66].

ryngeal carriage have been conducted (author's unpublished data). PnCRM7 vaccine was licensed in February 2000 and is now routinely recommended for infants and children in the US.

Not only have AI/AN children been at high risk for IPD, but adults in these populations have also suffered disproportionately from IPD. Data from prospective, population-based laboratory surveillance on the Navajo reservation have shown rates of IPD among Navajo adults that were three- to five-fold higher than those of the general US population; among Navajos 18–64 years of age and >65 years of age the rates of disease were 56 per 100,000 population and 190 per 100,000 population respectively [64]. The reasons for the increased risk of pneumococcal disease among Navajo adults are unknown. A greater proportion of Navajos with IPD had an underlying medical risk factor compared with those in the general US population who developed IPD. A recent study of risk factors for IPD among Navajo has revealed that the high prevalence of underlying medical conditions is a significant contributor to the high rates of IPD [authors' unpublished data]. Prevention efforts have focused on the use and promotion of the licensed and recommended 23-valent polysaccharide vaccine (PPV23).

Until recently, no studies had determined the effectiveness of PPV23 in these US populations at high risk for pneumococcal disease. In an observational study, the effectiveness of PPV23 among Navajo adults was evaluated using a case control and an indirect cohort analysis [67]. All patients with IPD between 1989 and 1998 for whom serotype information was available were included. Collection of case information and selection of controls was conducted through review of medical charts. The overall effectiveness of PPV23 in this population was 26% (Tables 6 and 7). Among individuals with specific risk factors for pneumococcal disease, the efficacy of PPV23 was lower than that estimated for the overall population. For those with diabetes, the effectiveness was 15% (95% CI: −116%, 67%), while among patients with alcoholism, the effectiveness was −5% (95% CI: −141%, 54%). The Johns Hopkins Center for American Indian Health has recently completed additional studies on the epidemiology of adult pneumonia in AI populations [authors' unpublished data].

Table 6
Vaccine effectiveness for ≥2 doses of PPV23 vs. no vaccination, adjusted for underlying medical conditions, for all case patients and for case patients with disease due to vaccine serotypes

Cases included	Case patients		Control patients		%Vaccine effectiveness (95% CI)
	N	# Vaccinated (%)	N	# Vaccinated (%)	
All serotypes	61	20 (33)	199	80 (40)	40 (−27 to 72)
Vaccine serotypes	31	10 (32)	94	37 (39)	43 (−79 to 82)

Data from: Benin et al. [67].

Table 7
Effectiveness of PPV23 vaccination among Navajo adults by the indirect cohort analysis

Vaccination status	Total no.	Vaccine-type disease	Nonvaccine-type disease	Vaccine effectiveness[a] (%) (95% CI)
Vaccinated, ≥1 PPV23	129	20 (33)	19 (15)	35 (−33 to 69)
Not vaccinated	149	10 (32)	15 (10)	

Date are no. (%) of case patients, unless otherwise indicated. OR, odds ratio; PPV23, 23-valent pneumococcal polysaccharide. Data from: Benin et al. [67].

[a] Vaccine effectiveness = (1 − adjusted matched OR for vaccination) × 100%.

A major focus of attention to determine the potential impact of conjugate pneumococcal vaccines on both children and adults has been on the effect of vaccines on colonisation in the nasopharynx. These studies of nasopharyngeal carriage have set out to describe the epidemiology of pneumococcal carriage in an era of widespread use of conjugate pneumococcal vaccine including examining: (1) the natural history of pneumococcal carriage, (2) the impact of PnCRM7 on carriage among vaccinees, unvaccinated children and adult household members, (3) the duration of protection of PnCRM7 against carriage in vaccinated children, as well as (4) the association between serum anti-capsular antibody concentration and protection against nasopharyngeal acquisition of pneumococcus. A longitudinal, observational study among American Indian families is currently underway to describe the impact of long-term, routine, community-wide PnCRM7 vaccine use on carriage among vaccinees as well as unvaccinated household members including adults. Knowledge gained from these studies may prove useful for anticipating the disease patterns in these communities and for the introduction and use of pneumococcal conjugate vaccines in other settings, particularly those characterised by high rates of carriage and disease, such as in developing countries.

2. Summary

American Indian and Alaska Native children, families, and communities have made important scientific contributions to the understanding and subsequent control strategies for numerous infectious diseases of importance in their communities such as diarrhoea, trachoma, hepatitis B, *H. influenzae*, and *S. pneumoniae*. Moreover, these studies of the epidemiology and efficacy of vaccines against these pathogens have had an impact far beyond the communities in which they were conducted. These studies have resulted in remarkable contributions to global health. Notably, these trials have led to the licensure of several vaccines which, among popula-

tions where they are routinely used, are preventing every day tens of thousands of deaths and disability in children. The effective use of these treatment and prevention interventions evaluated among Native American communities has a legacy that reaches far beyond the participants in the studies, to members of their communities in years following the studies and far beyond to children, families, and communities in other Native American populations and around the world.

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