ELSEVIER

Vaccine 19 (2001) 4592–4594

Vaccine

www.elsevier.com/locate/vaccine

Short communication

Natural immunity to haemophilus influenza b in infancy in Indian children

Jacob M. Puliyel*, Kishore S. Agarwal, Fuad Abed Abass

Department of Pediatrics, St Stephens Hospital, Tis Hazari, Delhi 110054, India

Received 21 January 2001; received in revised form 26 March 2001; accepted 14 May 2001

1. Introduction

The routine use of haemophilus influenzae type b (Hib) vaccines has virtually eliminated Hib meningitis and other invasive Hib diseases in industrial countries [1]. The cost of the vaccine is considerable. In the United States of America the cost is approximately $5.60 per dose (1998 price: source, National Immunisation Program CDC) [1]. It has been suggested in *Nature Medicine* [2] that if developing countries could be induced to routinely use the vaccine and universal immunisation were the norm, sales of 500 million doses per year could be achieved and this would bring down the price of vaccination. For Hib this would mean four doses for each year's birth cohort, at 2, 4, 6 and 18 months [2]. As of now the vaccine is used mainly in developed countries. The above statement could be interpreted to mean that poorer countries must use the vaccine to bring down the price of vaccination in the West. The need for the vaccine in developing countries, however, has not been established. The Committee on Immunisation of the Indian Academy of Paediatrics feels that the vaccine is safe and effective and must be advised to parents who can afford it [3].

The incidence of Hib diseases is different in different regions. It is 6 per 100,000 in Asia compared to 109 per 100,000 in the Western Pacific and Oceanic countries [1]. In India Hib is not commonly identified and documented [4]. It is, however, suspected that the low reported incidence may be due to poor bacterial culture facilities [5]. The most systematic effort to circumvent this problem and find the true incidence of invasive Hib in India, was a prospective multi-hospital surveillance by the IBIS group. They employed meticulous culture methods in six large teaching hospitals, with a combined bed strength of 8187 beds, in the metropolitan cities of Delhi, Lucknow, Madras, Nagpur, Trivandrum and Vellore. After 24 months of this surveillance there were 58 isolates of *Haemophilus influenza* among 3441 cases of meningitis, pneumonia and sepsis [6]. Other reported studies available quote an incidence of 8–14% for meningitis and 7–15% for lobar pneumonia [7]. The carriage rate is not known, but high antibody titres are found in children from a young age and this may provide an insight into the lower rate of invasive Hib disease in India. In this communication we analysed the data available from India demonstrating these high antibody titres.

There is controversy about the titre at which anti-Hib polyribosylribitol phosphate (anti Hib-PRP) yields protection. Robbins et al. have argued that since invasive Hib disease is extremely rare in adults, they must all have protective concentrations of antibodies. Ninety-five percent of adult sera analysed had more than 0.04 μg/ml of anti-Hib polysaccharide and so they concluded that serum levels above 0.04 micro g/ml affords protection [8]. Makela et al. found levels more than 0.15 μg/ml in adults and used this as a cut off [9]. Santosham et al. [10] and Ambrosino et al. [11] tested passive immuno-prophylaxis for invasive Hib disease in high-risk populations and concluded that concentrations from 0.05 to 0.15 μg/ml are protective. Studies looking at the efficacy of vaccine against Hib have looked at the geometric mean titre (GMT) of anti Hib-PRP, as well as the proportion of children achieving antibody levels above the arbitrary cut-off of 0.15 μg/ml. In trying to elucidate why some communities are more immune than others, it may be pertinent to look at the GMT in the community rather than number of

* Corresponding author. Fax: +91-11-3932412.
E-mail address: puliyel@vsnl.com (J.M. Puliyel).

PII: S0264-410X(01)00222-5

individuals in each community having antibody levels above some arbitrary cut-off. We looked at the GMT of anti-PRP antibodies in different age groups in Indian children and tried to compare them with the West.

2. Pre-vaccination antibody titres

Table 1 shows anti-PRP antibody GMT studied in Indian children gathered from four separate studies [7,12–14]. The antibody titres were tested using a radio-immuno-assay by Pasteur Merieux in France in three of the studies [6,12,14]. The GMT in all age groups studied from India have been above 0.1 μg/ml and do not reach a susceptible nadir as in children in the West. One group of 103 children were tested between 1.5 and 4 months using ELISA technique by Wyeth-Lederle USA and this also showed a GMT of 0.124 μg/ml [13]. In the West, babies have a high GMT at birth which is said to reflect maternal antibody levels. These levels then fall progressively. The present understanding is that children under 2 years have poor immune response to capsular polysaccharide of Hib. Even children who develop invasive Hib infections, such as meningitis, often do not develop a substantial concentration of serum antibodies if they are under 18 months of age [15]. This leaves them vulnerable to infection after maternal antibody levels wane. The high levels of antibody at different ages through infancy and early childhood in India suggests that passive immunity lasts longer or that active antibody production takes place much earlier in Indian children.

Table 1
Pre-vaccination anti-PRP antibody titres (μg/ml)

Age group (months)	Number of children	Geometric mean titre (μg/ml)	Method used for anti-PRP estimation	Reference
2 months				
Group A	27	0.186	RIA	[12]
Group B	27	0.198	RIA	[12]
1.5–4 months	103	0.124	ELISA	[13]
1–12 months	27	0.3	RIA	[7]
12–24 months	25	0.21	RIA	[7]
16–24 months				
Group A	28	0.24	RIA	[12]
Group B	28	0.24	RIA	[12]
18–24 months				
Group A	88	0.167	RIA	[14]
Group B	35	0.153	RIA	[14]
24–36 months	23	0.3	RIA	[7]
36–48 months	9	0.55	RIA	[7]
48–60 months	16	0.94	RIA	[7]
>60–120 months	70	1.18	RIA	[7]

Table 2
Anti-PRP specific IgG antibody titres measured by ELISA in healthy Turkish children [16]

Mean age in months (range)	Geometric mean titres (μg/ml)	Number of infants with Anti–PRP concentration >0.15 μg/ml (%)
1.5	0.24	41 (64%)
2.5	0.21	32 (65.3%)
6.5	0.20	29 (53.7%)
13	0.22	32 (69.6%)

Similar findings were noted in Turkey by Tasten et al. [16] who investigated naturally acquired anti-PRP in healthy children during the first year of life. In a prospective longitudinal study they repeatedly tested anti Hib titres in a cohort of 64 children. The results, summarised in Table 2, show that the majority of infants have protective concentrations of anti-PRP from 1.5 to 13 months. They suggested that most of the infants studied had high concentrations of maternally transferred anti-PRP and that they acquire natural active immunity to Hib at an early age.

3. Post vaccination antibody titres

Table 3 depicts the post vaccination antibody levels in Indian children. After three doses of conjugated Hib vaccine, post vaccination GMT up to 31.48 μg/ml was observed. This is in contrast to anti-PRP antibody titres of 3.64–6.4 μg/ml achieved in children in the United States and Europe [17–20].

A study in Venezuela also demonstrated unexpectedly high antibody titres after immunisation of infants with PRP-T vaccine. Post-vaccination levels of 37.9

Table 3
Serological response to three doses of conjugated haemophilus influenza vaccine in infants given as primary immunisation along with their routine DPT/OPV immunisation

Number of children	Type of vaccine used	Post vaccination GMT	Reference
48	PRP–T		[7]
Group A = 24		11.97	
Group B = 24		31.48	
54	PRP–T		[12]
Group A = 27		18.75	
Group B = 27		13.00	

μg/ml were achieved [21]. A study of PRP-T vaccine in Chilean children found a high post immunisation GMT of 11.3 μg/ml [22].

T lymphocyte memory cells, if primed previously, are known to produce high antibody levels on exposure to the natural antigen or on giving booster vaccination [23]. The exaggerated response to primary vaccination in Indian children, seen alongside the high pre-vaccination levels, suggests that the children had been primed by natural infection and that the high pre-vaccination levels represent immunity acquired actively by the infant rather than transferred passively from the mother.

4. A possible explanation

Studies from the early 1970s may hold an explanation for this phenomenon. It is known that other bacteria have cross-reactive antigens to the Hib capsular polysaccharide. In an elegant experiment with burros, Bradshaw et al. [24] demonstrated the development of serologically specific precipitate antibodies to Hib, after immunisation of the animals with *Staphylococcus aureus* and *Bacillus subtillis*. Strains of Staplylcocci, Group D Streptococci, Diphtheroids and *Escherichia coli* have been found with cross-reactive antigens to Hib [24]. Robbins et al. [25] have demonstrated that infants show enhanced immune response to *H. influenzae* capsular polysaccharide when they have concurrent cross-reacting *E. coli* infection of the gut. Under these circumstances a rapid and sustained rise in antibody to Hib was noted. *E. coli* are ubiquitous in developing countries like India and their presence in the gut may have helped to stimulate antibody to Hib in the subjects reported [7,12–14].

Although the mechanism by which this is achieved is uncertain, these studies show that children in some developing countries posses protective levels of anti-Hib antibodies from an early age. There is thus a great potential for savings to be made in vaccination use in developing countries, if this finding is further substantiated.

References

[1] Levine OS, Schwartz B, Pierce N, Kane M. Development, evaluation and implementation of haemophilus influenzae type b vaccines for young children in developing countries: current status and priority actions. Pediatr Infect Dis J 1998;17(5):95–113.

[2] Anonymous. Forward living up to the legacy. Nature Med Vaccine Suppl 1998;4:475–6.

[3] John TJ. Newer vaccines: Like Marie Antoinette said, 'Let the poor eat cake' Reply. Indian Pediatr 1998;35:1246–9.

[4] Ayyagari A, Sharma P, Chakrabarti A, Agarwal KC. Isolation and detection of haemophilus influenzae from patients of respiratory tract infections and their antibiotic susceptibility pattern in Chandigarh. Indian J Chest Dis All Sci 1985;27:230–5.

[5] Kumar L, Ayyagari A. The etiology of lobar pneumonia and empyema thoracis in children. Indian Pediatr 1984;21:133–7.

[6] Steinhoff MC. IBIS. Invasive Haemophilus influenzae disease in India: a preliminary report of prospective multihospital surveillance. Pediatr Infect Dis J 1998;17:S172–5.

[7] Acharya D, Bhave S, Joshi V, Bavdekar A, Pandit A. Haemophilus influenzae type B vaccine in India: Need and timing, immunogenecity and tolerance. Indian Pediatr 1997;34:9–15.

[8] Robbins JB, Parke JC, Schneerson R, Whisnant JK. Quantitative measurement of 'natural' and immunization-induced Haemophilus influenzae type b capsular polysaccharide antibodies. Pediatrics 1973;7:103–10.

[9] Makela PH, Peltola H, Kayhty H, et al. Polysaccharide vaccines of group A *Neisseria meningitidis* and *Haemophilus influenzae* type b. J Infect Dis 1977;136:S43–50.

[10] Santosham M, Read R, Ambrosino D, et al. Prevention of haemophilus influenzae type b infections in high risk infants treated with bacterial polysaccharide immunoglobulin. New Engl J Med 1987;317:923–9.

[11] Ambrosino DM, Landesman SH, Gorham CC, Siber GR. Passive immunization against disease due to haemophilus influenzae type b: concentrations of antibody to capsular polysaccharide in high risk children. J Infect Dis 1986;133:1–7.

[12] Kumar A, Dutta AK, Saili A, et al. Immunogenecity and tolerance of H influenzae type b, tetanus toxoid conjugate vaccine given concurrently or in combination. Indian J Pediatr 1997;64:839–47.

[13] Phadke MA, Kulkarni MV, Sovani VB, et al. Immunogenicity study of Haemophilus influenzae type b conjugate vaccine in Indian infants. Indian Pediatr 1997;34:779–83.

[14] Acharya D, Desai A, Nanavaty N, et al. Evaluation of immunogenicity and tolerance of single dose Haemophilus influenzae type b (PRP-T) vaccine. Indian Pediatr 1995;32:1077–82.

[15] Michaels RH, Norden CW. Pharyngeal colonization with *H influenzae* type b: A longitudinal study of families with a child with meningitis or epiglottitis due to *H influenzae* type b. J Infect Dis 1977;136:222–8.

[16] Tastan Y, Alikasifoglu M, Ilter O, et al. Natural immunity to Haemophilus influenzae type b among healthy children in Istanbul, Turkey. Indian Pediatr 2000;37:414–7.

[17] Fraser DW. Haemophilus influenzae in the community and in the home. In: Sell H, Wright PF, editors. Haemophilus influenzae epidemiology, immunology and prevention of disease. New York: Elsevier, 1982:11–2.

[18] Dajani AS, Asmar B, Thirumoorthi MC. Systemic Haemophilus influenzae disease: an overview. J Pediatr 1979;94:355–64.

[19] Robbins JB, Schneerson R. Polysaccharide protein-conjugates: a new generation of vaccine. J Infect Dis 1982;161:321–32.

[20] Eskola J, Peltola H, Takala AH, et al. Efficiency of Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. N Engl J Med 1987;317:717–22.

[21] De Febres OC, Decker MD, Estopinan M, et al. Enhanced antibody response in Venezuelan infants immunized with Haemophilus influenzae type b tetanus toxoid conjugate vaccine. Pediatr Infect Dis J 1994;13:635–9.

[22] Ferreccio C, Clemens J, Avendano A, et al. The clinical and immmunologic response of Chilean infants to Haemophilus influenzae type b polysaccharide tetanus protein conjugate vaccine co-administered in the same syringe with diphtheria-tetanus toxoid-pertussis vaccine at two, four and six months of age. Pediatr Infect Dis J 1991;10:764–71.

[23] Granoff DM, Holmes SJ. Comparative immunogenecity of Haemophilus influenzae type b polysaccharide protein conjugate vaccines. Vaccine 1991;9:S30–4.

[24] Bradshaw MW, Schneerson R, Parke JC, et al. Bacterial antigens cross reactive with capsular polysaccharide of Haemophilus influenzae type b. Lancet 1971;1:1095–8.

[25] Robbins JB, Schneerson R, Argaman M, Handzel ZT. Haemophilus influenzae type b: Disease and immunity in humans. Ann Internal Med 1973;78:259–69.