

Variations in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND)

G Devereux, L Stelitano, C M Verity, A Nicoll, R G Will, P Rogers

Arch Dis Child 2004;**89**:8–12

Aims: To identify any UK children with variant Creutzfeldt-Jakob disease (vCJD) and obtain information about the causes of progressive intellectual and neurological deterioration (PIND) and the geographical distribution of cases.

Methods: The PIND Study uses the monthly surveillance card that is sent to all UK paediatricians by the British Paediatric Surveillance Unit. Case details are obtained from the reporting paediatricians by telephone interview, site visit, or self completion of a questionnaire. A paediatric neurology expert group then classifies the anonymised cases. The Communicable Disease Surveillance Centre (CDSC) provides mapping support.

Results: After five years and five months of surveillance, 1400 children had been reported. In the UK the majority of PIND cases had a confirmed diagnosis (comprising 99 different conditions); 505 "no cases" and 97 "outstanding" cases were excluded. A total of 798 PIND cases were included as follows: 577 with a confirmed underlying diagnosis; six with definite or probable vCJD, 51 who had undiagnosed PIND but were not thought to have vCJD, and 164 cases who were still under investigation. In some districts there were unexpectedly high numbers of PIND cases with a heterogeneous mixture of underlying diagnoses. In the five districts with the largest numbers of resident cases the majority not only came from a particular ethnic group but also had high reported rates of consanguinity.

Conclusions: In districts with large numbers of PIND cases there are major resource implications. These children and their families have complex problems and they need access to diagnostic facilities and appropriate service provision.

See end of article for authors' affiliations

Correspondence to:
Dr C Verity, Child Development Centre, Box 107, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK; christopher.verity@addenbrookes.nhs.uk

Accepted 23 May 2003

There are many diseases that cause progressive intellectual and neurological deterioration (PIND) in children. Although individual PIND conditions are relatively rare, children with PIND have special needs that can be very challenging and distressing for families and caregivers, requiring specialised planning and support.¹ The geographical distribution and social characteristics of children with PIND have not been described in the UK or elsewhere. To investigate this we used data from the PIND Study. The Study commenced in May 1997 and is expected to continue until at least April 2004. It uses active multi-source prospective surveillance to identify disorders causing progressive intellectual and neurological deterioration in children.

The Study is based at Addenbrooke's Hospital, Cambridge, and is carried out through the British Paediatric Surveillance Unit (BPSU) in collaboration with the Communicable Disease Surveillance Centre (CDSC) in London and the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) in Edinburgh. It was primarily designed to identify any cases of variant Creutzfeldt-Jakob disease (vCJD) that might occur in children,² but has also provided much information about the distribution of PIND.

The purpose of this paper is to describe and analyse demographic variation in the 798 children with PIND included in the Study between 1 May 1997 and 30 September 2002—a total of five years and five months surveillance. Many paediatricians have asked whether the Study will yield data that will be useful for planning clinical management and service provision, and it is hoped that the information in this paper will be helpful in this regard.

METHODS

The PIND study utilises the surveillance system established in 1986 by the British Paediatric Surveillance Unit (BPSU), part of the Royal College of Paediatrics and Child Health (RCPCH).³ All consultant paediatricians in the UK receive a monthly orange surveillance card on which they are asked to record whether or not they have seen any children with conditions that are currently under surveillance. Around 12 studies are under way at any one time. The BPSU office informs the surveillance groups about paediatricians who have reported cases. The groups then obtain the relevant information for their particular surveillance study directly from the reporting paediatrician. The return rates remain high—of 2097 paediatricians receiving the orange card in 2001, the response rate was 92.7%.⁴

Since May 1997, paediatricians have been reporting children with PIND according to a predefined case definition (see box). The data collection tool is a standardised questionnaire incorporating the child's clinical history and examination findings, birth and family history, and relevant investigation results. Data are collected in one of three ways: a telephone interview with the reporting paediatrician, a site visit to extract the information from the hospital notes, or a questionnaire posted to the paediatrician for self completion.

An expert group of six paediatric neurologists and a representative of the NCJDSU was established to support the research team and meets quarterly to review the often complex anonymised clinical data and to classify the cases according to diagnosis.

Colleagues at the CDSC have assisted the researchers by mapping the anonymised data using the postcodes of the

Case definition

Any child under 16 years of age at onset of symptoms who fulfils *all* of the following three criteria:

- Progressive deterioration for more than three months
- With
- Loss of already attained intellectual/developmental abilities
- And
- Development of abnormal neurological signs.

Excluding: Static intellectual loss, e.g. after encephalitis, head injury or near drowning.

Including:

- Children who meet the case definition even if specific neurological diagnoses have been made.
- Metabolic disorders leading to neurological deterioration.
- Seizure disorders if associated with progressive deterioration.
- Children who have been diagnosed as having neurodegenerative conditions but who have not yet developed symptoms.

Reports restricted to: Cases seen in the past month but including those whose conditions began earlier, i.e. including “old cases” of children in follow up (if seen in that month).

child’s residence to obtain the district of residence of each case of PIND.

Ethical consent for the Study was granted by the Public Health Laboratory Service Ethics Committee and the Cambridge Local Research Ethics Committee.

RESULTS

A total of 1400 children had been reported to the Study by 30 September 2002; 505 “no cases” and 97 “outstanding” cases

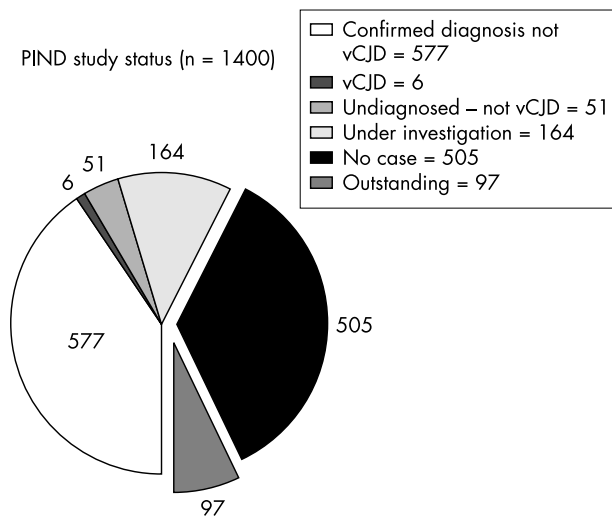


Figure 1 Total PIND cases by study category. “No cases” (n=505) and “outstanding” cases (n=97) were excluded from the analysis and are shown exploded. The remaining 798 cases were analysed according to the PHLs health district of residence as described in the text.

were excluded. A total of 798 cases were included in the analysis as follows (see fig 1):

- 577 children with a confirmed PIND diagnosis
- 6 children with definite or probable vCJD
- 51 children with undiagnosed PIND but not vCJD. These were children who had PIND but in whom no diagnosis had been made despite thorough investigation. Many had died. They formed a clinically heterogeneous group that had been extensively reviewed by the expert group, and none of them had the recognised clinical features described in vCJD.
- 164 children under investigation. This is a changeable group of PIND cases who are followed up on a six monthly basis and reallocated as appropriate. None of these cases were thought to have the clinical features of vCJD.

Analysis of 798 PIND cases

These were analysed according to district of residence, diagnosis, ethnicity, and consanguinity.

District of residence

The child’s district of residence was mapped according to the PHLs health districts. These have undergone some changes since the study first started, but for the purpose of these data constituted 126 districts. Only six districts had not reported any PIND cases. Numbers reported by district of residence were very variable—paediatricians in some units reported much larger numbers of PIND cases than the rest of the country. The five districts in which the largest numbers of PIND cases resided were Bradford (50 cases), Birmingham (31), East London & City (25), East Riding (22), and Berkshire (19). These are highlighted in fig 2.

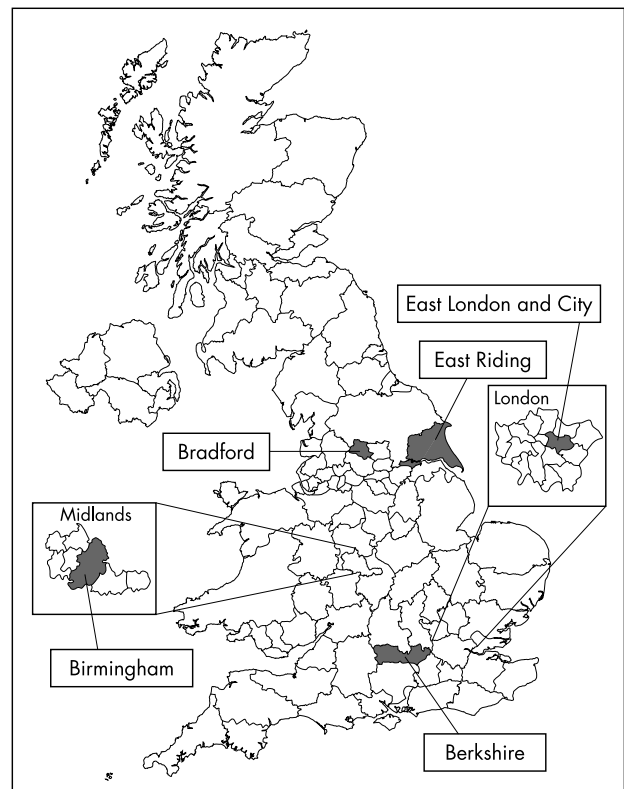


Figure 2 Map of the UK showing PHLs districts. The five highlighted districts are those in which the largest numbers of PIND cases resided.

Diagnosis

In the whole of the UK, there were 577 children (72%) with a confirmed PIND diagnosis, comprising 99 different conditions. The five most commonly occurring diagnoses in children with a definite PIND diagnosis were: mucopolysaccharidosis type III (Sanfilippo disease) (41 cases), adrenoleukodystrophy (32), late infantile neuronal ceroid-lipofuscinosis (31), mitochondrial cytopathies of unspecified type (30), and Rett syndrome (29) (see fig 3).

There was a heterogeneous mixture of PIND diagnoses in individual districts. For instance in Bradford, the district with the largest number of reported PIND cases, there were 32 children with PIND due to 15 different conditions. These were as follows (numbers of cases in brackets): GM2 gangliosidosis type O (Sandhoff disease) (7), Niemann-Pick disease type C (4), Cockayne syndrome (3), GM1 gangliosidosis (3), mitochondrial cytopathies of unspecified type (3), mucopolysaccharidosis type III (Sanfilippo disease) (3), unclassified leukodystrophies (2), Aicardi-Goutieres syndrome (1), metachromatic leukodystrophy (1), Refsum disease (1), neuraminidase deficiency (1), maple syrup urine disease (1), mucopolysaccharidosis IH (Hurler disease) (1), and arginase deficiency (1) (see fig 4).

Ethnicity

Cases were classified according to the following PHLS ethnic origin categories:

- White
- Black Caribbean
- Black African
- Black other
- Indian
- Pakistani
- Bangladeshi
- Chinese
- Other.

In the whole of the UK, the ethnic origin was known in 736 cases. A total of 487 (66%) of these children were white. The next largest group were Pakistani children—137 cases (19%). The other ethnic groups were much smaller (see fig 5).

In some districts the distribution of ethnic groups that made up the PIND cases was very different from others. For instance, in the district with the highest number of reported PIND cases, Bradford, 42 of the 49 cases with known ethnicity were Pakistani children (86%) and only three were White (see fig 6).

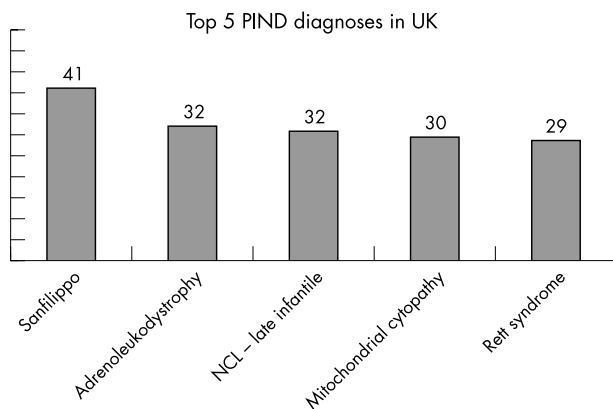


Figure 3 The five most frequently diagnosed causes of PIND in the UK.

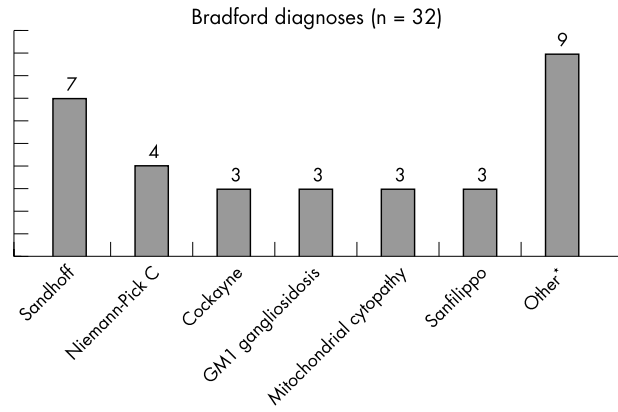


Figure 4 The causes of PIND diagnosed in Bradford.

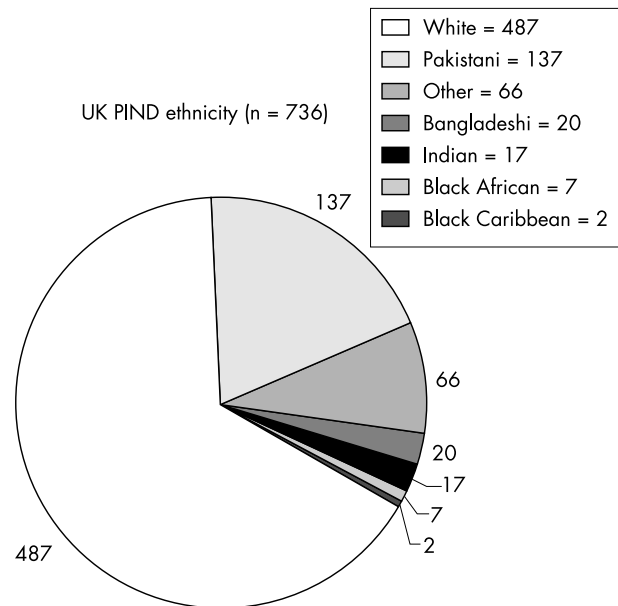


Figure 5 All UK PIND cases; ethnicity.

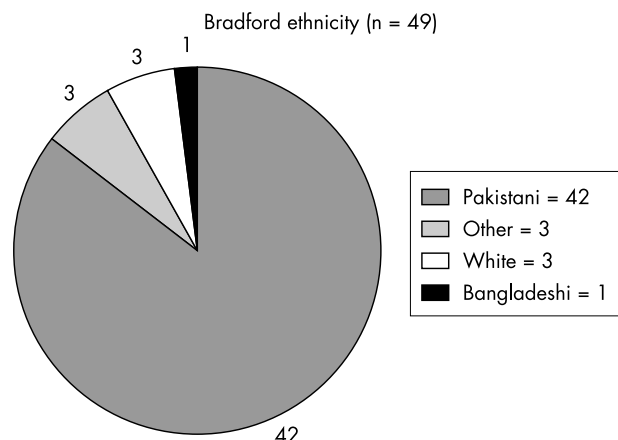


Figure 6 Bradford PIND cases; ethnicity.

Consanguinity

In the whole UK, 359 of the 798 PIND cases were not consanguineous, and there were 248 cases where consanguinity was not known. Of the 191 cases where consanguinity was known, 110 were Pakistani, 22 white, 7 Indian, 11 Bangladeshi, and 41 other (for example, Middle Eastern).

In the three districts with the largest number of reported PIND cases: Bradford, Birmingham, and East London & City, 66 of the 106 cases (almost two thirds) were consanguineous. Of these 66, 51 were South Asian (Pakistani and Bangladeshi) children. In Bradford, 37 of the 50 PIND cases were consanguineous (33 Pakistani, three other, and one Bangladeshi).

However, in East Riding (the fourth highest reporting district), 19 of the 22 children were white and there was only one case of definite consanguinity (in the only Pakistani child reported from that district). Eight were definitely not consanguineous and in 13 this was not known.

DISCUSSION

Surveillance issues

Five years and five months of surveillance have yielded valuable information about the distribution of disorders that cause PIND in the UK. The incidence and prevalence of PIND in the UK cannot be accurately extrapolated from the PIND study findings as these data reflect only those cases currently under the care of paediatricians, and complete case ascertainment through surveillance methodology is an unreasonable expectation.⁵⁻⁶ It is always a possibility that reporting fatigue will undermine case ascertainment, especially in a relatively long running surveillance study. However, in the PIND study there has been a relatively constant number of monthly reports throughout the surveillance period (median monthly reporting rate = 19).

The study has generated and maintained much interest and support. This could be partly due to the fact that paediatricians can choose how they wish to impart the relevant information, ranging from self completion of a study questionnaire, to carrying out a telephone interview, to choosing a visit from the research nurse who gathers the data from the notes. We also think that paediatricians are motivated to report cases because children with PIND generate a great deal of concern and there is a strong incentive to make a diagnosis. It has been reassuring to find that in the majority of cases a diagnosis has been made, which underlines the fact that many PIND cases are thoroughly investigated by district general paediatricians and their tertiary colleagues.

Reasons for variations in numbers reported by district

While we expected to find differences in the numbers of children reported by different UK districts, we were surprised to find such large numbers of PIND children in some districts. It is known that some ethnic groups in the UK have higher consanguinity rates, and it is also known that higher consanguinity rates contribute to an increased incidence of certain conditions, particularly autosomal recessive conditions.⁷⁻⁸ One UK study found that genetic disease causing disability was 10 times more common in Pakistani children than other ethnic groups.⁹ The PIND Study shows that in some districts relatively large numbers of PIND cases are reported, the majority of whom not only come from a particular ethnic group but also have high reported rates of consanguinity. In the three districts with the highest number of reported PIND cases: Bradford, Birmingham, and East London & City, 66 of the 106 cases (almost two thirds) were consanguineous. A previous UK study found a high prevalence of cerebral palsy in Asian families in Bradford,

with consanguineous marriages occurring in almost half of the families.¹⁰

In the whole UK, the majority of PIND cases (66%) were white children. The next largest group was Pakistani children (19%). The national census figures show that the Pakistani under 16 year old population in the UK is 1.8%.¹¹ In Bradford the difference from the national population figures was striking, and is further emphasised by the forecast that Bradford's population with Pakistani origins is likely to remain the largest ethnic minority, making up a fifth of the district's population by 2011.¹²

It was a possibility that the high numbers of PIND cases in certain districts might be due to one or two large kindreds with the same diagnosis. However, this has not been borne out by the study findings; for example, the 32 children in Bradford have 15 different PIND diagnoses and come from 24 different families. There was often more than one affected sibling within a family. For example, in Bradford, of the seven reported children with Sandhoff disease, there were three sets of two siblings from unrelated families, and one who was "known to be related to other Sandhoff cases in the Bradford district".

The distribution of disorders varied according to district, and in certain districts there was a marked difference from the general pattern. For example, three of the most commonly reported PIND conditions in the whole of the UK, the neuronal ceroid-lipofuscinoses, adrenoleukodystrophy, and Rett syndrome, were not evident in Bradford at all.

Consanguinity and ethnicity do not always account for large numbers of PIND cases in a district. For example, in East Riding (the fourth highest reporting district), there was only one case of definite consanguinity in the only Pakistani child reported from that district.

Aspects of care of children with PIND

The study has found that there is a large group of children with PIND, who have special health care needs and require the input of a highly specialised multidisciplinary team. The challenge of caring for children with special health care needs is well documented.¹³⁻¹⁵

Genetic counselling is increasingly important for the relatives of children with neurodegenerative disease. In this study, a significant number of children with autosomal recessive conditions, both diagnosed and undiagnosed, had received input from geneticists in the form of opinions and counselling. However, there are sensitive ethical and psychosocial considerations involved.¹⁶

The demands on the health service to provide for children with special needs are only likely to increase over time and planning for effective service delivery is becoming ever more crucial.¹⁷ It is hoped that the PIND study findings serve as a reasonably accurate portrayal of the characteristics and demography of children with PIND, and it is important to state that children with severe neurodegenerative conditions have been reported from all but six health districts in the UK. Although there were expected variations between districts, the very large numbers of PIND cases in some districts were unexpected. There are implications for those districts in terms of service provision and diagnostic facilities and it is hoped that the data in this paper will provide support for the appropriate allocation of resources.

ACKNOWLEDGEMENTS

Gillian Devereux gathered the study data, Lesley Stellitano designed and maintained the database, Christopher Verity, Angus Nicoll, and Robert Will planned the study, Pauline Rogers assisted with statistical input.

PIND surveillance is funded by the Department of Health and coordinated via the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health. Grateful thanks are extended

to Richard Lynn (BPSU Scientific Coordinator), John Stephenson (Research and Development Division, Department of Health), and Anya Leiva, Chris Lane, and Sheena Cramond of the Communicable Disease Surveillance Centre who provided mapping support and advice. We are also grateful to the paediatric neurologists who are members of the PIND Expert Group: Jean Aicardi, Peter Baxter, Stuart Green, Richard Robinson, Robert Surtees, and John Wilson. Last but by no means least, this surveillance would not have been successful without the support and cooperation of all the UK paediatricians who return the BPSU orange card, and we remain most grateful to them all.

Authors' affiliations

G Devereux, L Stellitano, C M Verity, A Nicoll, R G Will, P Rogers, Addenbrooke's Hospital, Cambridge, UK
A Nicoll, P Rogers, Communicable Disease Surveillance Centre, Health Protection Agency, London, UK
R G Will, National Creutzfeldt-Jakob Disease Surveillance Centre, Edinburgh, UK

REFERENCES

- Hunt A, Burne R. Medical and nursing problems of children with neurodegenerative disease. *Palliat Med* 1995;**9**(1):19–26.
- Verity CM, Nicoll A, Will RG, et al. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. *Lancet* 2000;**356**:1224–7.
- Verity C, Preece M. Surveillance for rare disorders by the BPSU. *Arch Dis Child* 2002;**87**:269–71.
- British Paediatric Surveillance Unit. *Annual Report 2001–2002*.
- Lynn R. Key issues in child health surveillance. *Proc R Coll Physicians Edinb* 2001;**13**:39–45.
- Dechlich S, Carter AO. Public health surveillance: historical origins, methods and evaluation. *Bull World Health Organ* 1994;**72**:285–304.
- Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups with particular reference to the effect of inbreeding. *Eur J Hum Genet* 1993;**1**:206–19.
- Hutchesson AC, Bundey S, Preece MA, et al. A comparison of disease and gene frequencies of inborn errors of metabolism among different ethnic groups in the West Midlands, UK. *J Med Genet* 1998;**35**:366–70.
- Morton R, Sharma V, Nicholson J, et al. Disability in children from different ethnic populations. *Child Care Health Dev* 2002;**28**(1):87–93.
- Sinha G, Corry P, Subesinghe D, et al. Prevalence and type of cerebral palsy in a British ethnic community: the role of consanguinity. *Dev Med Child Neurol* 1997;**39**:259–62.
- Office for National Statistics. *Census Data*, 1991.
- Anon. *Bradford population forecasts and information bulletin*. February 2000.
- Davidson EJ, Silva TJ, Sofis LA, et al. The doctor's dilemma: challenges for the primary care physician caring for the child with special health care needs. *Ambul Pediatr* 2002;**2**:218–23.
- Gravelle AM. Caring for a child with a progressive illness during the complex chronic phase: parents' experience of facing adversity. *J Adv Nurs* 1997;**25**:738–45.
- Davies H. Living with dying: families coping with a child who has a neurodegenerative genetic disorder. *Axone* 1996;**18**(2):38–44.
- Avard DM, Knoppers BM. Ethical dimensions of genetics in paediatric neurology: a look into the future. *Semin Pediatr Neurol* 2002;**9**:53–61.
- Roberts G. Supporting children with serious health care needs. Analyzing the costs and benefits. *Evaluation & the Health Professions* 2001;**24**:72–83.

ARCHIVIST

Cochlear implants and meningitis

Three firms in the USA make cochlear implants and nearly 10 000 American children have such a device. In June 2002 one of the manufacturers notified the US Food and Drug Administration of 15 reports of cochlear implant-associated bacterial meningitis. This firm's implants included a positioner, a small Silastic wedge intended to keep the electrode pressed against the medial wall of the cochlea, and it was suspected that the positioner might be implicated in the meningitis cases. These implants were recalled in July 2002 but cases of meningitis were also reported in children who had had implants made by the other two firms that did not have a positioner. Data have now been reported (Jennita Reefhuis and colleagues. *New England Journal of Medicine* 2003;**349**:435–45, see also perspective article, *ibid*: 421–3) about all 4264 children under 6 years of age who had a cochlear implant in the USA between 1 January 1997 and 6 August 2002.

Twenty-three children each had one episode of bacterial meningitis and three had two each. The causative organisms were *Streptococcus pneumoniae* (15 episodes), nontypeable *Haemophilus influenzae* (3), *H influenzae* type b (2), *Acinetobacter baumannii* (2), *Escherichia coli* (1), enterococcus (1), and unknown (5). The meningitis occurred within 30 days of implantation in nine children but the longest time from implantation to meningitis was 3 years. Eight children had otitis media at the time of presentation with meningitis. One child died. Three had the implant removed.

The incidence of pneumococcal meningitis (138 cases per 100 000 child-years at risk) was more than 30 times higher than in children of the same age in the US population. Use of a positioner was associated with 4.5-fold increase in meningitis compared with implants without a positioner. Children who had both a CSF leak during surgery and radiological evidence of a middle ear malformation had a ninefold increase in risk compared with other children with an implant.

The authors of this paper emphasise the importance of immunisation against pneumococcus and Hib and of prompt response to symptoms suggestive of meningitis and early treatment of otitis media in all children with a cochlear implant.