Medians and interquartile ranges of Beck's depression inventory 21 values in different glucose tolerance categories checked by oral glucose tolerance test in elderly Finns

	Normal glucose tolerance* (n=367)	Impaired glucose tolerance† (n=92)	Type 2 diabetes mellitus‡ (n=32)
Correlation between qualitative insulin sensitivity check index and Beck's depression inventory 21§	–0.037; P=0.492	–0.24; P=0.029	Not feasible
Beck's depression inventory 21 median (interquartile range)	5.0 (2.0-8.0)	6.0 (4.0-8.5)	6.0 (3.5-8.0)
Difference in median (95% confidence interval)	Control	1 (0 to 2)	1 (–1 to 2)
Wilcoxon rank-sum test P value	Control	0.015	0.380
		Control	0.639

*People with fasting glucose concentration of <6.1 mmol/l and 2 hour blood glucose concentration of <7.8 mmol/l in oral glucose tolerance test. Thus the normal glucose tolerance group includes also those with impaired fasting glucose (fasting glucose concentration 5.6-6.0 mmol/l).
†People with a fasting glucose concentration of <6.1 mmol/l and 2 hour blood glucose concentration of 7.8-11.0 mmol/l in oral glucose tolerance test.
‡ People with fasting glucose concentration of ≥6.1 mmol/l or 2 hour blood glucose concentration of ≥11.1 mmol/l in oral glucose tolerance test.
§Spearman partial correlation coefficient between qualitative insulin sensitivity check index and Beck's depression inventory 21 scores adjusting for body mass index, smoking, alcohol consumption, physical inactivity, sex, and basic education.

different levels of disturbed glucose metabolism, patients with type 2 diabetes and impaired glucose tolerance had higher depression scores (median 6.0 and 6.0) than those with normal glucose tolerance (5.0); the difference was statistically significant between impaired and normal glucose tolerance groups (table).

Comment

Insulin resistance (a low qualitative insulin sensitivity check index) and severity of depressive symptoms (Beck's depression inventory 21) were positively correlated, particularly in people with impaired glucose tolerance. Our findings are at variance with those of Lawlor and colleagues,[1] who suggested that a clinical diagnosis of diabetes in itself would be an explanation for their findings regarding diabetic patients. With our database, clinical diagnoses could not have affected the results, because we excluded patients previously diagnosed as having diabetes. Because in our study higher depression scores were already prevalent in those with impaired glucose tolerance without clinically manifest diabetes, our findings might be explained biologically—that is, by pathophysiological changes behind insulin resistance and depression.

Insulin resistance could develop as a consequence of an increased release of counter-regulatory hormones associated with depression.[2] This, however, is unconfirmed. The strengths of our study were that the qualitative insulin sensitivity check index has shown to be a reliable instrument in screening insulin sensitivity in epidemiological studies.[4] Also this was a population based study consisting of a representative sample of one whole age group. A limitation of our study is that the validity of the findings based on self reported Beck's depression inventory scales is inferior to those of structured diagnostic rating scales; thus, it cannot provide specific depression diagnoses. Neither could we test the causal hypothesis, because we did not know the full history of depression in the participants.

Contributors: MT conceived the study, reviewed the literature, and wrote the initial and subsequent drafts. SKK helped to conceive the study and revise the initial and subsequent drafts, and was overseer of the research group. JJ designed the statistical analyses, analysed the data, developed the figure, and helped draft the manuscript. ML and UR collected the data and contributed to the study design, interpretation, and revisions of the manuscript. VBMR helped revising the initial draft and contributed to revisions and discussions. MT is guarantor.

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Incidence of *Haemophilus influenzae* type b meningitis during 18 years of vaccine use: observational study using routine hospital data

Heikki Peltola, Eeva Salo, Harri Saxén

Correspondence to:
H Peltola
heikki.peltola@hus.fi

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Despite the spectacular success of *Haemophilus influenzae* type b (Hib) conjugate vaccines in the developed world,[1] failures have become more common in the Netherlands and the United Kingdom, where the incidence of invasive Hib diseases at age 0-4 years per 100 000 increased from 0.66 in 1998 to 2.96 in 2001.[2] An immunological defect is not to blame.

This increase in failure coincided with the change from whole cell pertussis to combined three component acellular vaccine (DTaP-Hib). This combination lowers Hib antibodies.[3] The clinical significance is unclear. Acellular vaccine cannot be blamed in the Netherlands, where whole cell vaccine was still used.[4] Both countries have been giving Hib vaccination at age 2, 3, and 4 months; a booster at 11 months is given in the Netherlands. Another characteristic in the United Kingdom is concomitant meningococcal group C

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conjugate. Replacement of serotypes other than Hib in severe diseases has also raised concern.

Because *H influenzae* meningitis in the Greater Helsinki area has been recorded since 1939, we had a unique opportunity to investigate any impact of vaccination.

Methods and results

Three paediatric hospitals have been dealing with severe infections here. We studied the records of *H influenzae* meningitis in 1939-2003. Of 454 children aged 0-4 years in 1980-5, only 0.2% (two cases, one of type a and one of type g) were caused by types other than Hib.

Three Hib conjugates have been used in Finland—diphtheria toxoid conjugate (PRP-D) in 1986-9, mutant diphtheria toxoid conjugate (HbOC) in 1988-9, and from 1994 onwards tetanus, toxoid conjugate (PRP-T) in 1990-3. Only three doses of Hib—at ages 4, 6, and 14-18 months—have been given since 1988.

No cases were found in 1991-4 (figure). In the next nine years, three Hib meningitides were found: in 1995 (a 6 year old girl with three doses of PRP-D), in 1999 (a 4 year old boy with three doses of HbOC), and in 2000 (a 4 month old boy vaccinated once only with HbOC).

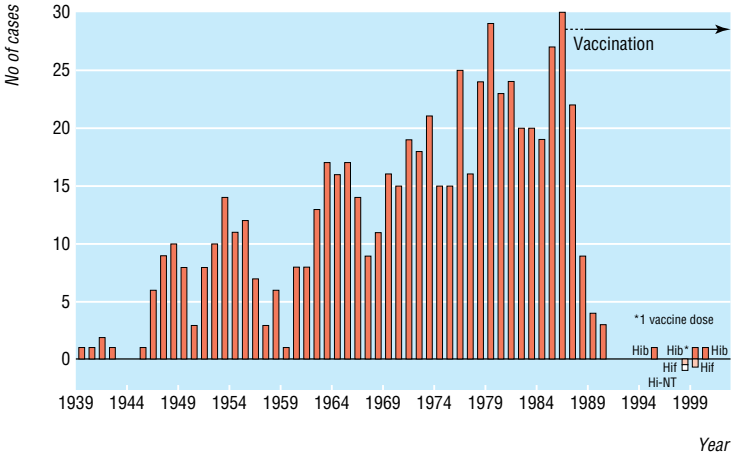
There were, however, three more cases of *H influenzae* meningitis, two caused by Hif, one by a non-typable strain. No immunological defect was seen.

Comment

Despite fears that the effectiveness of Hib conjugate was declining, excellent protection from Hib meningitis has been maintained with only three doses across Scandinavia. In 2003, five vaccine failures were identified in Finland, but despite this, we think our approach—keeping at least two months between the first two doses and giving the third as a late booster—is a good compromise.

The acellular pertussis component has been blaimed for the Hib vaccine failures, but those have not become more common after implementation of pentavalent or hexavalent vaccines in Germany. The lower anti-polysaccharide concentration alone cannot be the only explanation. The Dutch schedule was changed from immunisation at 3, 4, and 5 months to 2, 3, and 4 months, and this small change in timing might have played a role, despite a late booster. Significance of the concomitant use of meningococcal group C conjugate in the United Kingdom is not yet settled.

Epidemiological data are probably more relevant than antibody measurements, which are not always correctly interpreted. The surrogate antipolysaccharide antibody concentrations of 0.15 µg/ml for short term and of 1.0 µg/ml for long term likely protection (determined by our group)[5]—still taken by many as surrogate markers for clinical effectiveness—applied to Hib polysaccharide; for conjugate vaccines, we simply do not know what the "protective" antibody concentrations are. Instead, what we can quantify is a vaccine's clinical effectiveness. We think a later booster is important at the age when vaccine induced antibodies are declining.



Cases of Hib meningitis in the Greater Helsinki area (current population >1 million), 1939-2003. No reincrease in the incidence has been found since wide scale vaccination began in 1986. Hib=*Haemophilus influenzae* type b; Hif=*H influenzae* type f; Hi-NT=non-typable *H influenzae*. Three different Hib vaccines have been used over the years

What is already known on this topic

The official recommendation is four doses for the most widely used *Haemophilus influenzae* type b (Hib) conjugate vaccines; despite this, Finland has been using only three vaccine doses since 1988 with excellent clinical effectiveness

What this study adds

Two Hib vaccine doses in early infancy with a late booster is efficacious and may practically eliminate Hib meningitis

Attention should be paid to the clinical effectiveness of Hib conjugates rather than surrogate antibody measurements, which we often cannot interpret correctly

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Helsinki University Children's Hospital, Hospital for Children and Adolescents, PO Box 281, 00029 HUS, Helsinki, Finland

Heikki Peltola *professor of infectious diseases*

Eeva Salo *consultant of pediatric infectious diseases*

Harri Saxén *consultant of pediatric infectious diseases*