Association between type 1 diabetes and Hib vaccine

Causal relation is likely

EDITOR—We initiated and funded a collaborative study with Tuomilehto on the effect of the *Haemophilus influenzae* type b vaccine on type 1 diabetes and found that the data support a causal relation (paper submitted for publication). Furthermore, the potential risk of the vaccine exceeds the potential benefit. We compared a group that received four doses of the vaccine, a group that received one dose, and a group that was not vaccinated. The cumulative incidence of diabetes per 100 000 in the three groups receiving four, one, and no doses of the vaccine was 261, 237, and 207 at age 7 and 398, 376, and 340 at age 10 respectively.

Karvonen et al's analysis is not rational, and their conclusion is not supported by our data.[1] Their calculations of relative risk are also misleadingly low, and we urge readers to check them. Most researchers would compare the group who received four doses with the group that was not vaccinated or the two vaccinated groups with the group that was not vaccinated. The results of both comparisons reach significance. The cumulative difference in cases of type 1 diabetes per100 000 between those receiving four doses and those who were not vaccinated is 54 cases (P = 0.013) at 7 years and 58 cases at 10 years (P = 0.029; single tail Fisher test). The relative risk is 1.26 at 7 years. The cumulative difference between those receiving four doses or one dose of the vaccine and those who were not vaccinated is 42 cases (P = 0.016) at 7 years and 47 cases at 10 years (P = 0.028).

The rise in diabetes, just one potential adverse effect, exceeds the benefit of the vaccine, which has been estimated to prevent seven deaths and 7-26 cases of severe disability per 100 000 children immunised.[2] Even the difference in cases of diabetes between the groups receiving four doses and one dose exceeds the mean expected benefit. Temporal changes in the incidence of diabetes do not explain the differences since there were an extra 31 cases of type 1 diabetes per 100 000 children aged 5-10, and the incidence of diabetes in this group had been stable for about 10 years before this.[3] Furthermore, sharp rises in diabetes have been recorded in the United States[4] and the United Kingdom[5] after the introduction of the haemophilus vaccine.

Public health officials want to avoid scaring the public, but they risk depriving damaged children of compensation. Denials of safety issues may erode public confidence, especially since diabetes induced by the vaccine may be avoided by starting vaccination a few weeks earlier.

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1 Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study. *BMJ* 1999;318: 1169-72. (1 May.)
2 Peltola H, Kayhty H, Sivonen A, Makela H. Hemophilus influenza type B capsular polysaccharide vaccine in children: a double blind field study of 100 000 vaccinees 3 months to 5 years of age in Finland. *Pediatrics* 1977; 60:730-7.
3 Tuomilehto J, Virtala E, Karvonen M, Lounamen R, Pitkaniemi J, Reunanen A, et al. Increase in incidence of insulin-dependent diabetes mellitus among children in Finland. *Int J Epidemiol* 1995;24:984-92.
4 Dokheel TM. An epidemic of childhood diabetes in the United States. *Diabetes Care* 1993;16:1606-11.
5 Gardner S, Bingley PJ, Sawtell PA, Weeks S, Gale EA. Rising incidence of insulin dependent diabetes in children under 5 years in Oxford region: time trend analysis. *BMJ* 1997;315:713-6.

More research is still needed

EDITOR—I read Classen and Classen's comments in the *eBMJ*[1] [edited letter printed here, above] on the paper by Karvonen et al.[2] Classen and Classen question the way that the data in the paper were analysed and presented. They highlight the fact that in table 2 the relative risk of type 1 diabetes was only compared between cohorts 1 and 3 (those who did not receive any *Haemophilus influenzae* type b vaccine and those who received the vaccine at 24 months only) and cohorts 2 and 3 (those who received four doses of the vaccine from 3 months and those who received the vaccine at 24 months only). Why did Karvonen et al not give a comparison between cohorts 1 and 2 (those who did not receive any vaccine and those who received four doses from 3 months)?

Furthermore, in figure 1 of this paper (cumulative incidence of type 1 diabetes per 100 000 person years in Finnish children aged 10 or under) only the data for cohorts 2 and 3 were plotted. Why were the data for cohort 1 excluded? Could it be that including the data for cohort 1 on the graph would have allowed a more direct visual comparison between cohorts 1 and 2 to be made? And would this have then made it more difficult for Karvonen et al to convince casual observers that there is no link between the introduction of *H influenzae* type b vaccine and an increase in the incidence of type 1 diabetes?

The greatest increase in type 1 diabetes has occurred in children aged under 4 (fig 2),[2] which coincides with the period when *H influenzae* type b vaccine was introduced in the mid-1980s. This should raise our suspicions as to whether the vaccine could be responsible for this increase. Karvonen et al have dismissed the data as not being significant; however, the impact on the lives of a further 58 cases per 100 000 children at the age of 10 who will have to learn how to deal with a lifelong chronic disease such as type 1 diabetes should not be trivialised.

Further research would do well to focus on the incidence of type 1 diabetes before and after the introduction of *H influenzae* type b vaccination programmes in other countries, such as Australia, the United States, and the United Kingdom.

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1 Electronic responses. Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study. *eBMJ* 1999;318 www.bmj.com/cgi/content/full/318/7192/1169#responses (accessed 7 May 1999).
2 Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study. *BMJ* 1999;318:1169-72. (1 May.)

Radioiodine and thyroid eye disease

Routine steroid prophylaxis is not yet justified

EDITOR—The relation between treatment with radioiodine and thyroid eye disease, discussed in Walsh et al's editorial, troubles many endocrinologists and patients.[1] There have been concerns that the use of radioiodine for thyrotoxicosis due to Graves' disease may be associated with a deterioration in ophthalmopathy, raising the question of whether radioiodine is safe for patients with mild ophthalmic Graves' disease. This question has been addressed recently by Bartalena et al, who showed that there is a small but significant risk of deterioration in mild ophthalmopathy after the use of radioiodine and that this risk may be reduced by simultaneous administration of systemic glucocorticoids.[2]

Walsh et al go further and advocate that high dose prednisone, as used in Bartalena et al's trial, should be used routinely in all patients with mild ophthalmopathy who are to receive radioiodine, to reduce the risk of deterioration in eye disease. Surely this is not yet justified. No account has been taken of the appreciable adverse effects of giving prednisone for three months (typically 30-40 mg/day for the first month and then reducing over the next two months). In Bartalena et al's study under a tenth of patients (7/72) with mild pre-existing ophthalmopathy who received radioiodine had a deterioration that was more than transient and required treatment.

Routine use of glucocorticoids exposes all patients who receive them to important adverse effects, while the benefit is limited to a few. Certain clinical features (for example, mild but active or progressive ophthalmopathy) are likely to mark out those who are at risk. Further studies are needed to examine this and to determine the minimum dose and duration of glucocorticoid treatment that protects against deterioration of eye disease.

At present there is a case for limiting treatment with glucocorticoids to those who have an appreciable symptomatic worsening of ophthalmopathy rather than treating all