Key messages

- An association of intramuscular vitamin K prophylaxis and childhood cancer was not confirmed in a population based case-control study in Germany
- The study size was sufficient to detect a cancer risk of at least 1.55
- The cumulative evidence from this and previous studies almost excludes an association of intramuscular vitamin K prophylaxis and childhood cancer

had identical exposure to vitamin K. The observation of a higher nominal odds ratio for the comparison with local controls than for the comparison with state controls does not indicate that the overall results were biased by overmatching. Thirdly, comparison of too similar exposure groups: this objection was made by Passmore *et al*[14] with regard to the study of Ekelund *et al*.[7] In the Swedish study parenteral vitamin K prophylaxis was compared with oral prophylaxis only. This source of bias seems unlikely in our study as no significant association could be detected when the comparisons were confined to no prophylaxis versus parenteral vitamin K. Finally, insufficient blinding: the study design can almost rule out this kind of error. The case-control status was known only to the Mainz study centre, whereas the data collection and data entry were carried out in Düsseldorf. The two databases were not merged before the Düsseldorf database was completed. There were few if any chances for the nurses collecting the data to identify the case-control status during the process of data abstraction.

Information on a considerable number of confounders was collected in this study. Except for prematurity (left in the final model because of prior considerations) none of these was significantly associated with occurrence of cancer in childhood. As expected and plausible, the use of parenteral vitamin K prophylaxis was more common in premature babies or after operative delivery. None of these potential confounders, however, had any impact on the observed odds ratios after introduction into the logistic regression model.

The increased odds ratio observed for children aged 1-6 years with acute lymphatic leukaemia in comparison with local controls could not be explained by any of the potential confounders. Similar results were not found in comparison of this patient group with the state controls. We regard this as a chance result in subgroup analyses with multiple testing.

Like others[2-4 6 7] we are unable to confirm an increased risk of cancer associated with parenteral vitamin K prophylaxis. Most of the objections made with respect to the previous studies[5 14] cannot be maintained with respect to our results. The study therefore adds substantial evidence against a causal role of parenteral vitamin K prophylaxis in childhood cancer.

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Characteristics of orf in a farming community in mid-Wales

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Orf, a parapox viral infection of sheep and goats, has been recognised for over 200 years. Human cases were first recorded in the 1930s.[1] Transmission occurs by direct inoculation, commonly from the infected muzzles of hand reared lambs. The true incidence and prevalence of human orf is unknown, and workers familiar with the disease may not report infection. The typical target-like lesions most often affect the hands and heal spontaneously in six to seven weeks. Complications include secondary infection, erythema multiforme, and a generalised papulovesicular eruption.[2]

I recorded the morbidity from and the prevalence, seasonal variation, and complication rate of human orf in a farming community in mid-Wales, a population at risk of the disease.

Patients, methods, and results

Questionnaires were sent to 292 patients at this practice who worked with sheep and were aged between 16 and 65 on 1 January 1995. The results from 251 questionnaires were analysed (effective response rate 86%). Table 1 shows the high exposure to and recognition of orf in sheep. Nearly all respondents claimed to be able to recognise human orf. Almost a third (73) reported having had it, with over a third reporting previous infection in a household member. Of the 73 reported cases, 34 (47%) were in women and 39 (53%) in men. Over a fifth reported two or more attacks, the second attack mostly occurring within two years. Most respondents had had their first attack in their teenage or early adult

Table 1—*Exposure to, recognition of, and infection with orf in mid-Wales farming community*

	No (%) of respondents giving positive replies
All respondents (n = 251)	
Would you recognise orf in a sheep?	237 (94)
Have you ever handled sheep with orf?	224 (89)
Would you recognise orf if you caught it yourself?	196 (78)
Have you ever had orf?	73 (29)
Have any other members of your household had orf?	86 (34)
Would you be prepared to take part in further research on the treatment of orf?	205 (82)
Patients who had had orf (n = 73)	
How often have you had orf?	
Once	58 (80)
Twice	10 (14)
More than twice	5 (7)
What was the length of time between attacks?	
1 Year	3 (20)
2 Years	6 (40)
3 Years	2 (13)
>3 Years	4 (27)
How old were you when you had orf?	
Teenager	21 (29)
In 20s	18 (25)
In 30s	14 (19)
In 40s	15 (21)
In 50s	4 (5)
In 60s	1 (1)
What time of year did you have orf?	
Spring	38 (52)
Summer	22 (30)
Autumn	10 (14)
Winter	3 (4)
Did you consult a doctor?	56 (77)

life, which is in keeping with starting work on the family farm. Most cases (60/73 (82%)) occurred in spring or summer. In addition, I identified 58 separate episodes of orf infection from general practice records. Thirty four (59%) occurred in April, May, and June—19 (33%) in May alone (table 1).

Sixteen respondents (22%) reported an accompanying red blotchy rash; erythema multiforme, toxic erythema, or allergic reaction was recorded in the general practice notes in nine cases (12%). Eight respondents (11%) indicated that they had blisters on their arms, body, face, or mouth when they had had orf. Widespread vesicular eruption was confirmed from the records in only three cases (4%). All of these had preceding erythema multiforme. Of the 24 people (33%) whose work was affected, four reported problems for less than a week, 11 for one to two weeks, and nine for more than two weeks. Eleven patients (15%) had time off work: three for less than one week, three for one to two weeks, and five for more than two weeks.

There were no reports of human to human spread.

Comment

Orf is common in flocks in mid-Wales. Most people who work with sheep can recognise both animal and human infection, but self diagnosis and lack of effective treatment could explain why almost a quarter of patients with orf chose not to consult a doctor. One episode of orf may[3] or may not[4] confer life long immunity. Although a fifth of my respondents reported two or more attacks, infection declined with increasing age. The seasonal variation correlated with the end of the lambing season.

The mechanism of the papulovesicular eruption is not understood, but such a dramatic rash is unlikely to be ignored by both patient and doctor. The hands are most commonly infected (occasionally the face), which explains why patients' jobs are affected and they lose time at work. Most attacks occur at the busiest time of the farming year, and illness is clinically significant. As there is no effective treatment, further evaluation of simple preventive measures such as wearing gloves and isolation of infected sheep needs to be carried out, although costs and practical considerations may prove difficult to overcome.

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Childhood leukaemia and intramuscular vitamin K: findings from a case-control study

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Exposures before birth and in early life have long been thought to be important determinants of cancer in children. Anxiety about the neonatal administration of vitamin K was raised in 1992, when Golding *et al* linked intramuscular, but not oral, vitamin K with childhood malignancy.[1] Of particular concern was the 2.65-fold increased risk of leukaemia.[1] Much debate ensued, and, although Golding's findings have not been confirmed elsewhere,[2-4] much public anxiety remains. We present the findings relating to vitamin K from a case-control study designed to investigate associations between leukaemia and prenatal and neonatal exposures.

Subjects, methods, and results

Cases comprise children (0-14 years) diagnosed with leukaemia whose mothers' obstetric notes are stored at the John Radcliffe Hospital, Oxford (born 1951 or later), the Rosie Maternity Hospital, Cambridge (born 1956 or later), and the Royal Berkshire Hospital, Reading (born 1969 or later). Of the eligible cases identified by the Childhood Cancer Research Group,[5] records covering delivery were found for 90% and obstetric notes for 85%. Two controls per case (matched on sex, hospital, and year and month of birth) were randomly selected from registers of all births held at the relevant hospitals. Multiple pregnancies, children with chromosomal anomalies, and babies who died before discharge were omitted. Delivery, obstetric, and neonatal records were abstracted by midwives using specially designed structured forms. Results are given for acute lymphoblastic leukaemia alone and all leukaemias combined. Findings are presented in two ways: firstly, by what was written in the notes (deriving route from hospital practice when it was not recorded); and, secondly, by what could be imputed from hospital policy. To ensure comparability with the results of