Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany

Submitted by
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Abstract

Objective—To confirm or refute a possible association of parenteral vitamin K prophylaxis and childhood cancer.

Design—Population based case-control study. Comparison of vitamin K exposure in children with leukaemia or other common tumours with two control groups.

Setting—State of Lower Saxony (north western part of Germany); case recruitment from the German childhood cancer registry.

Subjects—272 children with leukaemia, nephroblastoma, neuroblastoma, rhabdomyosarcoma, and tumours of the central nervous system diagnosed between 1 July 1988 and 30 June 1993; children were aged between 30 days and 15 years at diagnosis. 334 population based controls without diagnoses of cancer matched to the leukaemia cases for age and sex.

Main exposure measures—Parenteral vitamin K prophylaxis (intramuscular and subcutaneous) versus oral and no vitamin K prophylaxis.

Results—An association between parenteral vitamin K exposure and childhood cancer (leukaemias and other tumours combined) could not be confirmed (odds ratio 1.04, 95% confidence interval 0.74 to 1.48). For leukaemias the observed odds ratio was only 0.98 (0.64 to 1.50) (comparison of leukaemia cases with local controls 1.24 (0.68 to 2.25); state controls 0.82 (0.50 to 1.36)). These odds ratios remained almost unchanged when several potential confounders were considered in the logistic regression model.

Conclusions—This population based study adds substantial evidence that there is no association between parenteral vitamin K and childhood cancer.

Introduction

The report of a twofold increase of the risk of cancer in childhood after parenteral vitamin K prophylaxis in the neonatal period by Golding *et al* in 1992¹ has caused concern worldwide. From the analyses of time trends in incidence of cancer in relation to the use of parenteral vitamin K prophylaxis a twofold increase of the cancer risk seemed unlikely,²⁻⁴ but a lower, still important risk could not be excluded.⁵

Two major studies have been published since; neither has confirmed Golding's findings, but each had specific problems. The results in the study from the United States were obtained from 48 cases of cancer in children born in 1959-66, when a different vitamin K preparation was used and when other risk factors may have been relevant.⁶ Ekelund *et al* analysed presumed rather than documented vitamin K exposure and compared the effect of parenteral vitamin K prophylaxis with oral prophylaxis only.⁷

We therefore performed a case-control study of children born in 162 different obstetrics hospitals from 1975 to 1993 when only one vitamin K preparation—the same as the one used in Golding's study in two Bristol hospitals—was licensed for neonatal vitamin K prophylaxis.

Patients and methods

This study was performed as part of a population based case-control study⁸ to explore possible causes of

childhood leukaemia in Lower Saxony, a state with 1.25 million children under the age of 15 in north western Germany. Further details on the study design, methodology, and a summary of results are presented elsewhere.⁹ Cases of acute leukaemia were from the German Childhood Cancer Registry,¹⁰ which covers about 95% of the incidence since 1986. Children eligible for the study were born after 1 July 1975, aged between 30 days and 15 years at diagnosis, diagnosed with cancer between 1 July 1988 and 30 June 1993, and resident in the state of Lower Saxony at diagnosis. A total of 218 children with leukaemia fulfilled these criteria. (The number of patients under 15 with acute leukaemia in Lower Saxony diagnosed between July 1988 and June 1993 was 225 (an incidence of 3.9 per 100 000 children, which is slightly below the national rate of 4.3).) For 204 of these the doctors who had been responsible for the cancer treatment were willing to ask the parents to collaborate in the study.

CONTROLS AND OTHER CANCERS

Selection of controls was performed with the help of the local government offices for registration of residents: for each leukaemia case one control was selected from the municipality where the patient lived at the time of diagnosis (local control) and a second one from a municipality selected at random in the state of Lower Saxony by means of a population weighted sampling scheme (state control). Controls were matched by sex and date of birth. If one control family refused to collaborate in the study or did not return the questionnaire within three months another control family was invited. The number of selected and invited families in each of the two control groups (305 local and 308 state controls) exceeds the number of selected leukaemia cases ($n = 204$). In some instances control families returned the questionnaire after more than three months, when another family had already been invited. This accounted for more than one control for some cases. As an additional study group all cases of brain tumours, nephroblastoma, neuroblastoma, and rhabdomyosarcoma in the registry were checked for eligibility according to the same criteria as for leukaemia cases. A total of 246 tumour cases fulfilled these eligibility criteria, and for 216 of these the doctors responsible for the cancer treatment were willing to ask the parents to collaborate in the study. The tumour cases had been selected as a third control group for the leukaemia study but were used as additional "cases" in the vitamin K and childhood cancer study. Therefore no population based controls were selected for the tumour cases. The tumour cases were not matched with the leukaemia cases.

QUESTIONNAIRES

Questionnaires were sent by the doctors (cases) or by the study centre (controls) and were returned to the Mainz study centre (childhood leukaemia study) for completion and for any additional information to be obtained by a telephone interview. During the telephone interview parents were asked to sign a form with written consent to allow us to access the birth records of their children. The names and hospitals of delivery of the cases and controls were mailed to

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BMJ 1996;313:199-203

Düsseldorf, where the data abstraction from the birth records in the delivery hospitals was coordinated. For children born outside the state of Lower Saxony the obstetric hospitals were contacted only if they were in West Germany or the former Democratic Republic of Germany, whereas hospitals abroad were excluded.

Paediatric nurses used a comprehensive questionnaire, modelled on the questionnaire used by Golding *et al.*¹ The case-control status of each child was disclosed by the study centre in Mainz only when all data had been entered on to the database. It is extremely unlikely that the children's status was identifiable by the nurses during the data abstraction process. The information was obtained from the mothers' records held in the departments of obstetrics; these records never contain any follow up information on the children beyond the neonatal period; the nurses were not based at the hospital where they analysed the records; the only people the investigators contacted in the hospitals they visited were the obstetrician, her or his secretary, and the midwife. These people were unlikely to know about cancer in a child born in the hospital several years before the nurses' visits.

The coding instruction for the nurses was to report the information regarding all potential risk factors for childhood cancer on the questionnaire as "yes" or "no" only, when this information was explicitly stated in the records. If no information was explicitly stated—for example, regarding exposure to x rays or smoking—they ticked "unknown."

The only vitamin K preparation used for neonatal vitamin K prophylaxis in Germany from 1975 to 1992 was the cremophor preparation manufactured by Roche. The accuracy of the assessment of the vitamin K exposure was graded as, firstly, dose and route of vitamin K prophylaxis documented either in the child's record or in the delivery book; secondly, the vitamin K exposure of the child nearest the index baby in the delivery book with the same route of delivery and same perinatal morbidity (presumed failure to document vitamin K prophylaxis for the index case); thirdly, a nurse, midwife, or doctor who worked in the unit at the time when the child was born told us what kind of vitamin K prophylaxis the respective child would have received given the birth weight and route of delivery; and, finally, a nurse, midwife, or doctor who did not work in the unit at the time when the child was born told us what kind of vitamin K prophylaxis she or he believed the respective child would have received given the birth weight and route of delivery. The nurses were instructed to try to obtain the information in hierarchical order: if no information (vitamin K given "yes" or "no") was found in the birth records the delivery book was considered; if no information was found in the delivery book the record of a comparable child was used, and so on. Vitamin K exposure was considered "unknown" in children for whom nothing was recorded nor could be remembered.

ANALYSIS

The statistical analyses included χ^2 testing and logistic regression models for calculation of odds ratios, P values, and 95% confidence intervals. The odds ratios were calculated with the SAS 6.08 procedures PROC LOGISTIC¹¹ and PROC PHREG.¹² Conditional logistic regression analysis was used to compare leukaemia cases with local controls (1:1 matching). Because of failure to get access to informative birth records in all cases and corresponding local controls, only 107 matched pairs were available for this analysis. On the basis of prior considerations the odds ratios were calculated with adjustment for social class and prematurity. As informative records were available for some state or local controls with no informative records on the corre-

Table 1—Proportions of cases and controls selected for study for whom vitamin K exposure could be assessed

Detail	Cases (leukaemia/ tumours)	Controls (local/state controls)
Selected and invited for study	420 (204/216)	613 (305/308)
Questionnaire and telephone interview	320 (159/161)	425 (219/206)
Permission to analyse birth records	295 (147/148)	376 (194/182)
Birth records accessible	277 (138/139)	353 (180/173)
Information regarding vitamin K prophylaxis available	272 (136/136)	334 (174/160)
Source of the information on vitamin K prophylaxis:		
Birth record	194 (90/104)	211 (110/101)
Delivery book	2 (1/1)	4 (3/1)
Comparable child	9 (3/6)	6 (4/2)
Individual recall	63 (40/23)	109 (55/54)
Presumed practice	4 (2/2)	4 (2/2)

sponding cases, we included these controls for some analyses to increase the statistical power.

For the comparison of leukaemia cases versus state of controls there was no matching on place of residence; the municipality for the recruitment of control was selected by a random procedure. As many cases were identical in sex and age at diagnosis, the exact 1:1 assignment of cases and controls would not reflect the random selection of the municipalities. Instead of a 1:1 matching a frequency matching (n:m) on the variables age and sex was used. For controls "age" was defined as the time from birth to the date of diagnosis of the corresponding case.

In the analyses matching for age was used instead of the original matching variable date of birth. For cases the time from birth to the date of diagnosis and for controls the time from birth to the date of diagnosis of the corresponding case were defined as age. The conditional regression analysis included 136 leukaemia cases and 160 state controls. We included type of region, social class, and prematurity as potential confounders. The same type of analysis was used for the comparison of the leukaemia cases (n = 136) with the combined control group (n = 334) and for the combined cancer cases (n = 272) compared with all controls (n = 334). For analysis of the tumour cases we used all 334 controls that had been recruited for the study (including the local controls with no information for corresponding cases). This comparison was performed by unconditional logistic regression with adjustment for age, sex, type of region, social class, and prematurity. All these regression models were also performed for the subset of all those children, where the information concerning vitamin K exposure came from birth records or delivery books. To account for further possible but not prespecified confounders several additional risk factors were considered in the analyses.

Results

The paediatric oncologists sent the questionnaire to 420 of 464 eligible children with leukaemia and other tumours. The proportions of these cases and the selected controls invited to collaborate, whose birth charts could be analysed and were informative regarding the vitamin K prophylaxis, are listed in table 1. A smaller proportion of the controls (61%) than of the cases (70%) returned the questionnaire, were interviewed, and gave permission for the data abstraction from the birth records. The proportions of cases and controls whose birth records could be accessed were identical (94%). In 2% of the cases and 5% of the controls whose records were accessible no information regarding vitamin K exposure could be obtained. For 72% of the cases and 64% of the controls the vitamin K exposure status could be abstracted from birth records and delivery books

Fig 1—Proportions of controls given parenteral vitamin K prophylaxis (intramuscular or subcutaneous) by year of birth

(table 1). If no written information was available individual recall of "which vitamin K prophylaxis the child would have received" was the main source of information (table 1).

The documented and presumed prevalence of parenteral vitamin K prophylaxis in controls changed by year of birth (fig 1). In 1989 there was an increase to 95%, compared with a fluctuation between 20% and 60% in the years 1978-88. Additionally, the documentation of parenteral vitamin K prophylaxis in the infants' birth records became almost complete after 1988.

Parenteral vitamin K had been administered in 176 cases (intramuscular 147; subcutaneous 28) and 205 controls (174; 30). Two children who had been given both oral and parenteral vitamin K were attributed to the parenteral vitamin K group (one case, one control); 372 children (173 cases, 199 controls) received only one parenteral dose (< 1 mg four cases, two controls; 1 mg 149 cases, 178 controls; >1 mg 20 cases, 9 controls). Nine children received two or more parenteral doses of 1-2 mg vitamin K. Oral prophylaxis with 1-3 mg vitamin K had been given to 40 cases (once 28, twice or more 12) and 49 controls (once 40, twice or more 9). The distribution of the oral vitamin K doses was 1 mg in 13 children (9 cases, 4 controls), 2 mg in 69 children (28 cases, 41 controls), and 3 mg in 7 children (3 cases, 4 controls); 136 children had not received any vitamin K prophylaxis (56 cases, 80 controls).

Associations between the vitamin K exposures "intramuscular and subcutaneous" versus "oral or none" and childhood cancer were analysed for all

categories of vitamin K exposure for cases of leukaemia or other tumours and all cancers combined in comparison with the different control groups mentioned in the methods section to perform analyses similar to those in the study of Golding *et al*¹ with maximal statistical power (table 2). In the comparison of the leukaemia cases with the local controls, only pairs with information regarding vitamin K exposure available for both cases and corresponding controls were considered in the 1:1 analysis. Therefore 29 leukaemia cases and 67 local controls were not taken into account.

In the analyses no significant differences regarding the use of parenteral vitamin K prophylaxis in the neonatal period were found between the different case and control groups. Surprisingly the odds ratio with local controls, who were likely to have been born in the same hospitals (1.24), was higher than with the state controls (0.82), who had been born in different hospitals. The 1:1 analysis of leukaemia cases versus local controls was based on 46 discordant pairs (26 exposed cases with unexposed controls). If the two control groups were pooled and were compared with the leukaemia cases the odds ratio was close to 1.0 (0.98). The odds ratio for the comparison of tumour cases with both control groups showed no significant difference (1.19). In the comparison of all cases with all controls the odds ratio was 1.04.

To check whether these associations would be changed if the analyses were confined to definitely documented vitamin K exposures, these analyses were repeated for the cases and controls for whom vitamin K prophylaxis had been documented in birth records or delivery books (table 3). The results, however, remained almost unchanged, with the exception of the leukaemia cases versus local controls, for whom the odds ratio increased to 2.0 (95% confidence interval 0.69 to 5.97). This analysis, however, was based on only 54 matched pairs (16 discordant pairs; for 11 of these the case was exposed and the control was not exposed), which is also reflected by the wide confidence interval.

The results remained almost unchanged when unconditional regression analysis was used for the comparison of leukaemia and tumour cases versus local and state controls: in the analyses for all degrees of certainty of vitamin K exposure the odds ratio was 1.06 (0.79 to 1.41); in the analyses with information from the birth records or delivery books the risk estimate was 0.97 (0.61 to 1.52). In these analyses we adjusted for sex, age, social status, type of region, and prematurity. The results were almost identical when no adjustment for type of region and social status was made. In additional analyses we used year of birth as a matching variable instead of age. The results were almost identical.

Most cases of leukaemia in children aged 1-6 were common acute lymphatic leukaemias. To assess a

Table 2—Parenteral versus oral or no vitamin K prophylaxis in children with leukaemia, other tumours, and controls; estimation of vitamin K exposure including all degrees of certainty

Comparison between groups	No (%) of cases exposed	No (%) of controls exposed	Odds ratio* (95% confidence interval)	Type of analysis	P value†
Leukaemia cases (107) v local controls (107)	69 (65)	63 (59)	1.24 (0.68 to 2.25)	Conditional (1:1)‡	0.24
Leukaemia cases (136) v state controls (160)	85 (63)	102 (64)	0.82 (0.50 to 1.36)	Conditional (m:n)§	0.78
Leukaemia cases (136) v local and state controls (334)	85 (63)	205 (61)	0.98 (0.64 to 1.50)	Conditional (m:n)§	0.54
Tumour cases (136) v local and state controls (334)	91 (67)	205 (61)	1.19 (0.77 to 1.83)	Unconditional¶	0.22
Leukaemia cases and tumours (272) v local and state controls (334)	176 (65)	205 (61)	1.04 (0.74 to 1.48)	Conditional (m:n)§	0.40

*Calculated from multivariate logistic regression analysis.

†One sided test.

‡Adjusted for social class and prematurity.

§Adjusted for type of region, social class, and prematurity.

¶Adjusted for age, sex, type of region, social class, and prematurity.

Table 3—Parenteral versus oral or no vitamin K prophylaxis in children with leukaemia, other tumours, and controls; information of vitamin K exposure from the birth record or delivery book

Comparison between groups	No (%) of cases exposed	No (%) of controls exposed	Odds ratio* (95% confidence interval)	Type of analysis	P value†
Leukaemia cases (54) v local controls (54)	42 (78)	36 (67)	2.03 (0.69 to 5.97)	Conditional (1:1)‡	0.10
Leukaemia cases (91) v state controls (102)	70 (77)	80 (78)	0.87 (0.43 to 1.78)	Conditional (m:n)§	0.65
Leukaemia cases (91) v local and state controls (215)	70 (77)	160 (74)	1.12 (0.61 to 2.05)	Conditional (m:n)§	0.36
Tumour cases (105) v local and state controls (215)	76 (72)	160 (74)	0.90 (0.572 to 1.56)	Unconditional¶	0.64
Leukaemia cases and tumours (196) v local and state controls (215)	146 (75)	160 (74)	0.94 (0.59 to 1.50)	Conditional (m:n)§	0.61

*Calculated from multivariate logistic regression analysis.

†One sided test.

‡Adjusted for social class and prematurity.

§Adjusted for type of region, social class, and prematurity.

¶Adjusted for age, sex, type of region, social class, and prematurity.

potential carcinogenic effect of parenteral vitamin K prophylaxis in this relatively homogenous subpopulation the respective subgroup analyses were carried out. The (adjusted) odds ratio for cases of acute lymphatic leukaemia versus local and state controls combined was 1.22 (0.69 to 2.15, $P = 0.25$), for the comparison with state controls 0.99 (0.52 to 1.90; $P = 0.51$), and for cases of acute lymphatic leukaemia versus local controls 2.28 (0.94 to 5.54; $P = 0.03$). The last result was based on 25 discordant pairs, in 17 of which the case was exposed and the control was unexposed. There was no difference regarding the source of the information on vitamin K prophylaxis between cases and controls. For 50 cases (74%) and 53 controls (78%) the information came from the birth record.

We also performed all analyses for parenteral prophylaxis versus no prophylaxis alone to account for a bias from a potential carcinogenic effect of oral vitamin K. These revealed slightly decreased odds ratios for all but one of the comparisons (data available on request).

The following potential confounders of the association between parenteral vitamin K prophylaxis and childhood cancer were considered: x ray exposure in pregnancy (abdomen, thorax, or teeth), hospital admission in pregnancy, smoking or drinking in pregnancy, mode of delivery (vaginal, forceps, caesarean section), drugs given during delivery (pethidine, peridural anaesthesia, pudendal blockage, systemic anaesthesia, oxytocin), low birth weight for gestational age, phototherapy, BCG vaccination, type of feeding, referral to a paediatric ward, residence in urban or rural regions, and social class. No significant differences were detected for any of these factors between cases and controls. We also tested whether these factors were associated with the type of vitamin K prophylaxis. The only significant associations observed were: predominantly parenteral vitamin K in operative deliveries, premature and low birthweight infants, and babies referred to the paediatric ward. None of these potential confounders, however, accounted for meaningful changes of the associations of vitamin K prophylaxis and childhood cancer when tested with logistic regression models. The potential confounders low birth weight (≤ 2500 g) and referral to a paediatric ward were included in the regression model for the comparisons of leukaemia cases versus local controls. The odds ratios were 0.31 (0.05 to 1.79) for low birth weight, 1.57 (0.60 to 4.16) for referral to a paediatric ward, and 2.91 (0.37 to 22.67) for prematurity. The odds ratio for parenteral versus oral or no vitamin K prophylaxis remained nearly unchanged (1.17; 0.64 to 2.16) when these potential confounders were included in the model. Similarly the odds ratio for parenteral vitamin K prophylaxis remained almost

unchanged in the analyses where the information on vitamin K exposure could be obtained from the birth records or delivery books (2.02; 0.68 to 6.01). In the analyses where only children aged 1-6 years with acute lymphatic leukaemia were considered the odds ratio of these cases versus local controls after adjustment for these potential confounders was 2.12 (0.87 to 5.19; $P = 0.05$).

Discussion

In our study we could not confirm the association of parenteral vitamin K prophylaxis and childhood cancer observed by Golding *et al.*¹ This may be due to differences in the study designs. We had the opportunity to perform a population based study with 606 children born in 162 different obstetric hospitals. Documented information on vitamin K prophylaxis regarding both dosage and route of administration was available for most children, whereas the Bristol study was carried out in two hospitals only and route of the vitamin K administration often had to be inferred from knowledge of the hospital policy.¹

Some further differences between the studies might be relevant. The years of birth included in the Bristol study were 1965 to 1987 compared with 1975 to 1993 in our study. Additionally, the period for the recruitment of cancer cases was only five years compared with 20 years in the Bristol study.

Apart from these differences in design our study was well suited to confirm or refute the results of the Bristol study in an independent setting. Similar types and proportions of cancers were included in our study and the same vitamin K preparation was used. As in the Bristol study the prevalence of the exposure of parenteral vitamin K had changed over time. The increase from 70% to 95% after 1988 followed national recommendations for parenteral vitamin K prophylaxis issued in late 1986.¹³ With an average prevalence of parenteral vitamin K exposure of 63% and 606 informative birth records the sample size was sufficient to detect an increased odds ratio of 1.55 or more (one sided $P \leq 0.05$ and $\beta = 0.8$).

We considered several sources of bias which may account for failures to reproduce the Bristol results. Firstly, uncertain vitamin K exposures: the certainty of the information on vitamin K exposure in our study was recorded for each individual case. It seems unlikely that our results are attributable to the inclusion of cases or controls with uncertain vitamin K exposures as the same results were observed when the analyses were confined to documented exposures only. Secondly, overmatching: within the group of local controls 39 study participants were born in the same hospitals as the corresponding cases. Of these, 25 cases and controls

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.

We thank the obstetricians in Lower Saxony for their cooperation in giving us access to the birth records of the children involved in this study. This study would not have been possible without the help of the paediatric nurses, Marlies Brüncke, Frauke Hentschel, Ute Peters, and Ellen Völlmecke, who travelled far to visit all delivery hospitals to scrutinise the birth records for valid information on a considerable number of parameters. Dr Gerald Draper's comments on a previous version of the manuscript were extremely helpful.

Funding: Deutsche Krebshilfe project No 70529 and the state of Lower Saxony.

Conflict of interest: None.

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(Accepted 11 April 1996)

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

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BMJ 1996;313:203-4