Geographical variation in anophthalmia and microphthalmia in England, 1988-94

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Abstract

Objective: To investigate the geographical variation and clustering of congenital anophthalmia and microphthalmia in England, in response to media reports of clusters.

Design: Comparison of pattern of residence at birth of cases of anophthalmia and microphthalmia in England in 1988-94, notified to a special register, with pattern of residence of all births. Three groups studied included all cases, all severe cases, and all severe cases of unknown aetiology.

Outcome measures: Prevalence rates of anophthalmia and microphthalmia by region and district, and by ward population density and socioeconomic deprivation index of enumeration district grouped into fifths. Clustering expressed as the tendency for the three nearest neighbours of a case to be more likely to be cases than expected by chance, or for there to be more cases within circles of fixed radius of a case than expected by chance.

Results: The overall prevalence of anophthalmia and microphthalmia was 1.0 per 10 000 births. Regional and district variation in prevalence did not reach statistical significance. Prevalence was higher in rural than urban areas: the relative risk in the group of wards of lowest population density compared with the most densely populated group was 1.79 (95% confidence interval 1.15 to 2.81) for all cases and 2.37 (1.38 to 4.08) for severe cases. There was no evidence of a trend in risk with socioeconomic deprivation. There was very little evidence of localised clustering.

Conclusions: There is very little evidence to support the presence of strongly localised environmental exposures causing clusters of children to be born with anophthalmia or microphthalmia. The excess risk in rural areas requires further investigation.

Introduction

In early 1993 media reports alleged clusters of anophthalmia and microphthalmia in England, and postulated that these might be linked to exposure to the pesticide (fungicide) Benomyl (DuPont, Wilmington, DE).[1] This was not the first time that alleged clusters of anophthalmia and microphthalmia had been reported in relation to environmental exposure: earlier reports dating from 1986 investigated clusters of microphthalmia in connection with two high temperature waste incinerators in Wales and Scotland.[2 3]

Immediate assessment of the English clusters was complicated by two factors. Firstly, there was a lack of diagnostic detail in the reports, which meant that an expected prevalence of the conditions could not be confidently asserted.[4] Secondly, there was the so called Texas sharpshooter problem (a Texan fires randomly at a barn door and subsequently draws a bull's eye in the densest cluster of bullet holes), a usual dilemma in the post-hoc assessment of clusters. Even on a random, and therefore non-uniform, spatial pattern it is possible to draw boundaries around apparent clusters of cases in such a way that the density of the cases in that area far exceeds expectation.[5] However, this has no statistical validity without reference to the background pattern of all cases from whom the clusters were identified.

We report on the results of a study set up in response to public concern to establish the presence or absence of any geographical variation in anophthalmia and microphthalmia, including large scale regional variation, excess prevalence in rural areas, or localised clustering. The analysis is based on a register of all cases of anophthalmia and microphthalmia born in England in 1988-94, which was established for the purposes of this study.[6] The time period was chosen to overlap as far as possible with the period of concern and to collect enough cases for geographical analysis, but not to go back too far and risk major underascertainment of cases in earlier years.

Subjects and methods

Data

Our study is based on a register of all cases of anophthalmia and microphthalmia born in England in 1988-94. The methodology by which the register was established is described elsewhere.[6] There were 444 cases registered, excluding cases of trisomy 13 and holoprosencephaly or cyclops.[6]

As there is no formal cut off point between mild microphthalmia and the normal eye it was expected that mild microphthalmia might show considerable geographical variation due to diagnostic and reporting differences alone. Severity of microphthalmia was based on the information supplied by clinicians in specially designed questionnaires.[6] A subgroup of 237 (53.4%) severe cases was defined by excluding 113

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Table 1 Number of cases (all and severe) of anophthalmia and microphthalmia, prevalence per 10 000 births, and proportion of cases of unknown severity by region of residence in England, 1988-94

	All cases		Severe cases		
Region	No	Prevalence/10 000 (95% CI)	No	% Severity unknown	Estimated prevalence/10 000* (95% CI)
Oxford	41	1.6 (1.2 to 2.2)	19	17	0.9 (0.6 to 1.5)
Trent	50	1.2 (0.9 to 1.5)	32	19	0.9 (0.6 to 1.3)
South Western	31	1.1 (0.8 to 1.6)	15	19	0.7 (0.4 to 1.1)
East Anglia	20	1.1 (0.7 to 1.7)	12	10	0.7 (0.4 to 1.3)
Northern	28	1.0 (0.7 to 1.4)	15	14	0.6 (0.4 to 1.1)
South East Thames	35	1.0 (0.7 to 1.4)	20	12	0.7 (0.4 to 1.1)
North West Thames	34	1.0 (0.7 to 1.4)	13	41	0.6 (0.3 to 1.1)
Yorkshire	33	1.0 (0.7 to 1.4)	22	12	0.7 (0.5 to 1.1)
West Midlands	48	0.9 (0.7 to 1.3)	23	23	0.6 (0.4 to 0.9)
North Western	36	0.9 (0.7 to 1.3)	20	25	0.7 (0.4 to 1.1)
Wessex	23	0.9 (0.6 to 1.3)	11	13	0.5 (0.3 to 0.9)
South West Thames	24	0.9 (0.6 to 1.3)	12	25	0.6 (0.3 to 1.0)
North East Thames	26	0.7 (0.4 to 1.0)	14	31	0.5 (0.3 to 0.9)
Mersey	14	0.6 (0.4 to 1.1)	9	21	0.5 (0.2 to 1.0)
Not known	1	—	0	—	—
Total	444	0.98 (0.89 to 1.07)	237	21	0.68 (0.60 to 0.78)

*Prevalence estimated assuming that proportion of severe cases in additional cases of unknown severity is same as proportion in cases of known severity.

(25.5%) mild cases and 94 (21.2%) cases where the severity of microphthalmia was unknown.[6]

A further subgroup of 189 (79.7%) severe cases of unknown aetiology was defined by excluding 48 (20.3%) cases with known aetiology from the severe subgroup. The aetiology was established independently by a medical geneticist (Robin Winter) based on information obtained in questionnaires. The 48 cases included those with a syndrome of genetic origin, a family history strongly suggestive of genetic origin, bilateral conditions with parental consanguinity, and maternal infection.

The Office for National Statistics supplied postcoded birth registration data for the entire study period. There were 4 538 790 live births during 1988-94.

Postcodes of cases and all births allowed geographical localisation (grid reference with 100 m resolution) and assignment to census enumeration districts or wards where necessary. Cases were postcoded to residence at birth but in 33 (7.4%) cases (including 10 (4.2%) severe cases) the address at birth could not be obtained from the notification process.[6] Of all births from the Office for National Statistics' database, 12 616 (0.3%) were without valid postcodes.

Cases and births were grouped by regional health authority and district health authority of residence at birth according to the health authorities' boundaries before 1994 (table 1). In one (0.23%) case the region was unknown and in 14 (3.2%) cases the district was unknown. The urban or rural nature of the area of residence was determined using the population density of the 1991 census ward of residence. Wards were classed into five groups by dividing at quintiles of population density (table 2). Three per cent of births were in the group with the lowest population density, the proportion in this rural group in individual regions ranging up to 11% in East Anglia. As a validation of the main urban and rural analysis, an indicator of the urban or rural (dichotomous) nature of 1991 census enumeration districts was obtained from the Office for National Statistics. According to this indicator, 9% of births occurred in a rural setting. The state of socioeconomic deprivation of the enumeration district of residence was assessed according to the deprivation index developed by Carstairs.[7] This was standardised to Great Britain, and five socioeconomic groups derived corresponding to fifths of enumeration districts.

The estimated prevalence of severe cases was calculated by assuming that the proportion of such cases among cases of unknown severity was the same as the proportion of severe cases among those of known severity. For statistical analysis the denominator (number of births) rather than the numerator (number of cases) was manipulated in these estimations to avoid false inflation of statistical significance.

Statistical analysis

Comparison of prevalence of anophthalmia and microphthalmia across regions and groups defined by population density and deprivation was informed by the Pearson and Armitage χ^2 tests, and where necessary adjusted for confounding using Poisson regression. Variation in underlying prevalences across regions and across districts was estimated by the Martuzzi-Hills method,[8] which removes the random sampling variation expected in small numbers. This variation is expressed as the 5th to 95th centile range of prevalence ratios, relative to the overall prevalence. Expected numbers were calculated in each district of residence (for all cases and severe cases), stratified for region and population density fifth.

We used two tests of localised clustering: Cuzick-Edwards[9] and Diggle-Chetwynd.[10] For both these tests we used three controls per case randomly chosen from all births. For each case the Cuzick-Edwards test counts the number of other cases in its k nearest neighbours

Table 2 Number of cases (all, severe, severe of unknown aetiology) of anophthalmia and microphthalmia and prevalence per 10 000 births, by urban or rural residence (measured by population density)

				All cases		Severe cases		Severe cases of unknown aetiology	
Residence group	Population density (people/km^2)	Mean population density/km^2	No of births	No	Prevalence/ 10 000	No*	Estimated prevalence/ 10 000*	No*	Estimated prevalence/ 10 000*
1	0-59	25	151 681	22	1.45	16	1.29	12	0.97
2	60-316	148	424 416	45	1.06	26	0.73	24	0.67
3	317-1448	807	850 967	76	0.89	45	0.61	39	0.53
4	1450-3369	2344	1 328 077	124	0.93	63	0.59	50	0.47
5	⩾3371	5646	1 789 649	144	0.81	74	0.54	55	0.40
Not known	—	—	—	33	—	13	—	9	—
Total	—	—	4 538 790	444	1.0	237	0.66	189	0.53

*Prevalence estimated assuming that proportion of severe cases in additional cases of unknown severity is same as proportion in cases of known severity.

among all remaining cases and controls (we repeated with k = 1, 2, 3 … 8). For each case the Diggle-Chetwynd test counts the number of cases within k kilometres (we repeated with k = 1, 2, 3 … 50). Evidence for localised clustering exists if the sum of these counts is significantly greater than would be expected if cases were an independent sample of births.

The data included two pairs of siblings (all four cases were severe) who strongly influenced the results at short distances (1 nearest neighbour or 1 km distance). One of each pair was therefore removed from the clustering analyses on the basis that two members of a pair were probably not independent events. Both pairs had been excluded from the most restrictive subgroup of severe cases of unknown aetiology as most probably of genetic aetiology.

Results

The overall prevalence of anophthalmia and microphthalmia in England was 1.0 per 10 000 births. Table 1 shows the regional prevalence of all cases. Regional variation in prevalence did not reach statistical significance (P = 0.07 for all cases, P = 0.76 for severe cases). The 5th to 95th centile range of regional to national prevalence ratios for all cases estimated by the Martuzzi-Hills method was 0.83 to 1.22. There was no statistically significant heterogeneity in prevalence of all cases across districts (P > 0.20), with an estimated 5th to 95th centile range of the ratios of observed to expected numbers of cases of 0.83 to 1.19.

The prevalence of anophthalmia and microphthalmia increased with decreasing population density—that is, it was higher in rural areas (table 2). The relative risk was 1.79 (95% confidence interval 1.15 to 2.81) in the most rural group compared with the most urban group for all cases, and 2.37 (1.38 to 4.08) for severe cases (table 2). Among the 22 most rural cases, 36% (eight cases) were bilateral compared with an average of 35% (157 cases) overall. Poisson regression showed that urban and rural variation was reduced after controlling for region, both for all cases (relative risk for most rural fifth compared with most urban fifth was 1.61 (95% confidence interval 1.01 to 2.58)) and for severe cases (relative risk for most rural fifth compared with most urban fifth was 2.25 (1.29 to 3.95)). The validation analysis using the Office for National Statistics' urban and rural indicator showed that 20 out of 22 cases within the areas of lowest population density lived in enumeration districts classified as rural. Forty (9%) cases were classified as rural. The odds ratio for living in a rural enumeration district was 1.21 (0.85 to 1.72).

Table 3 Number of cases and prevalence per 10 000 births by socioeconomic deprivation group of residence

Socioeconomic deprivation group*	No of births	All cases	
		No	Prevalence/10 000 (95% CI)
1	821 494	79	0.96 (0.77 to 1.20)
2	869 718	72	0.83 (0.66 to 1.04)
3	884 855	93	1.05 (0.86 to 1.29)
4	917 304	72	0.79 (0.62 to 0.99)
5	1 038 769	92	0.89 (0.72 to 1.09)
Not classified or not known	6 650	36	—
Total	4 538 790	444	0.98 (0.89 to 1.07)

*Groups defined by dividing at quintiles of population of Great Britain: 1=most affluent, 5=most deprived.

Prevalence of anophthalmia and microphthalmia varied little by socioeconomic deprivation of enumeration districts (table 3). Relative risk for the most deprived group compared with the least deprived group was 0.92 (0.68 to 1.24). Tests for both heterogeneity and trend showed that the variation was easily explained by chance (P > 0.20).

Neither the Cuzick-Edwards (table 4) nor the Diggle-Chetwynd tests showed overall evidence of localised clustering at a national level (after removal of one of each of two pairs of siblings) whether or not controls were frequency matched to cases by population density fifth. Both tests were also performed for three regions separately: Trent, Northern, and Oxford. These regions had been selected a priori as having probably the most complete case ascertainment, or being areas of prior interest for clustering. The Cuzick-Edwards test showed no statistically significant clustering in these regions, while the Diggle-Chetwynd test showed statistically significantly more cases than expected within 2 km of an index case in Trent and within 50 km of an index case in the Oxford region. There was no evidence of clustering by the Cuzick-Edwards test within the most rural fifth or the two most rural fifths (table 4). The Diggle-Chetwynd test showed significant clustering in the most rural fifth only in the subgroup of severe cases of unknown aetiology, with more cases than expected within 7-9 km of other cases but based on only one case-case pair in Yorkshire. There was no significant clustering by this test when the two most rural fifths were considered.

Table 5 gives an empirical idea of the number of cases that occurred close together. Results are given for

Table 4 Observed number of cases of anophthalmia and microphthalmia within three nearest neighbours, number expected, and probability of exceeding the expected number by at least observed number, according to Cuzick-Edwards test

	All cases			Severe cases			Severe cases of unknown aetiology		
	No observed	No expected	P value	No observed	No expected	P value	No observed	No expected	P value
England:									
Overall	289	306.2	0.71	168	165.9	0.47	121	134.4	0.75
Control matched to case by population density fifth	287	306.2	0.72	151	165.9	0.74	125	134.4	0.68
Most rural fifth only	10	15.9	0.92	9	11.4	0.76	10	8.4	0.30
Two most rural fifths	51	49.1	0.44	30	30.9	0.53	34	26.4	0.08
Region:									
Trent	35	33.1	0.38	20	22.7	0.71	11	15.9	0.88
Oxford	27	26.6	0.47	10	12.2	0.72	8	9.9	0.72
Northern	23	20.4	0.29	6	10.7	0.92	4	7.7	0.90

Table 5 Counts of index cases of anophthalmia and microphthalmia according to number of other cases within specified distances* (by rural or urban residence of index case)

No of other cases*	Distance from index case (km)							
	1		5		10		20	
	Rural†	Urban‡	Rural	Urban	Rural	Urban	Rural	Urban
0	22	108	21	48	16	18	7	2
1	0	16	1	35	5	22	6	7
2	0	0	0	16	1	18	2	7
3	—	—	—	12	—	17	4	9
4	—	—	—	4	—	8	0	6
5	—	—	—	4	—	6	0	8
6+	—	—	—	5	—	35	3	85

†First fifth of population density (22 cases).
‡Fourth fifth of population density (124 cases).

the most rural fifth and second most urban fifth. Altogether, 48 cases had another case within 1 km and one case had two cases within 1 km. The maximum number of cases within 5 km of another case was eight, with 15 cases having 6-8 other cases within 5 km. The maximum number of cases within a 20 km radius urban area was 50. We may infer from the results of the tests for clustering that these numbers are close to those expected given the distribution of births and the prevalence of anophthalmia and microphthalmia.

Discussion

Aetiological significance of the findings

We found little or no evidence of large scale geographical variation or localised clustering in anophthalmia and microphthalmia during 1988-94. However, we did find a gradient in prevalence from urban to rural, with a 80% excess prevalence (95% confidence interval 15% to 181%) in the least densely populated wards compared with the most densely populated. Further analysis, whether by controlling for region or using a dichotomous indicator of urban or rural only, tended to reduce the strength of this association, but given the a priori hypothesis of a rural excess that we set out to test we cannot dismiss this finding.

Whether a rural excess, if real, is associated with pesticide exposure, as postulated in the media,[1] or one or more other environmental or genetic risk factors would need further investigation. The evidence for a causal link between exposure to pesticide and anophthalmia and microphthalmia is currently weak. Case reports of anophthalmia and microphthalmia do exist where mothers were exposed to pesticides in early pregnancy.[11 12] Since exposure to pesticides is common the significance of the case reports to date cannot be assessed. Two epidemiological studies could not find a relation between markers of Benomyl exposure and anophthalmia and microphthalmia. The first was an ecological study which correlated regional use of the product in Italy to the prevalence of anophthalmia and microphthalmia.[13] The second study identified a cohort of farming families in Norway in 1960-89 and found only one report of anophthalmia and microphthalmia in the medical birth register for the families that were potentially exposed.[14] Other epidemiological studies have examined congenital malformations in relation to markers of maternal exposure to pesticides, but the diversity of pesticides, methods of exposure measurement, and malformations in these studies make it difficult to draw valid conclusions. Animal experiments have induced anophthalmia and microphthalmia (as well as other congenital anomalies) with exposure to Benomyl at high doses,[15] but this has not been considered to constitute a risk to humans at lower doses.[16 17]

Probably the strongest evidence for an environmental aetiology for anophthalmia and microphthalmia concerns maternal infections, and lack of spatial clustering is of interest in this regard. The relation between maternal infections and anophthalmia and microphthalmia is well established for rubella, toxoplasmosis, cytomegalovirus, and varicella.[18 19] Other viruses are implicated but with less evidence, including parvovirus B19,[20 21] herpes simplex type 2,[22] Epstein-Barr,[23] and coxsackie A9.[24] Furthermore, there is evidence that influenza, fever, or hyperthermia may cause both malformations of the central nervous system and microphthalmia.[25–28] A specific effect of hyperthermia as a cause of anophthalmia and microphthalmia is supported by animal experiments.[25 29] Hyperthermia may be a potentiating coteratogen in association with other exposure (including chemicals).

Our finding of lack of spatial clustering suggests that if a large proportion of cases can be attributed to maternal infection then either this infection must not show strong spatial clustering or it must cluster in both space and time in such a way that clustering cannot be detected at a spatial level only. Further study of the anophthalmia and microphthalmia register will investigate variation in prevalence over time and space simultaneously in relation to known variations in maternal infections and pesticide use.

Other risk factors described in the literature for anophthalmia and microphthalmia include solvent misuse and exposure to *x* rays or drugs such as thalidomide, isotretinoin, warfarin, and alcohol.[19 30] Anophthalmia and microphthalmia are also associated with a wide range of genetic syndromes,[31] both chromosomal and monogenic, and it is likely that when a genetic syndrome is not evident, genetic susceptibility through one or more genes nevertheless plays a part in the response to environmental exposure.

We could find no association between prevalence of anophthalmia and microphthalmia and socioeconomic deprivation. Whatever the main risk factors are in determining the occurrence of anophthalmia and microphthalmia it seems they are not strongly related to socioeconomic factors.

Data quality and potential artefacts

The geographical analysis that we performed depends for its validity on the quality of the underlying data. As reported elsewhere,[6] we believe that about 15% (80) of cases may not have been reported to the register that we established, and that it is probable that these included mainly mild microphthalmia and children who did not survive their first year of life. It is difficult to establish a register retrospectively although our use of multiple sources of notification overcame this to a large extent. No source, even paediatricians who had seen the majority of cases, reported more than one quarter of cases to the register.[6] Underascertainment can have two main effects: to reduce the overall case number and thus statistical power (where 15% underascertainment is not a serious problem), and to introduce spurious geographical variation due to geo-

Key messages

- Clusters of anophthalmia and microphthalmia in England have been alleged in the media, with hypothesised links to environmental exposure such as pesticides
- To answer concerns about clustering a register has been established of all cases of anophthalmia and microphthalmia born in England in 1988-94
- There is no large regional or district variation in prevalence
- Rural areas have a roughly twofold excess in prevalence, which requires further confirmation and investigation
- There is very little evidence for localised clustering in England in 1988-94

graphical variation in ascertainment. Since we found little or no regional or district variation or clustering we doubt if these results would essentially have changed with complete ascertainment. The theoretical possibility that underascertainment might obscure geographical variation and clustering seems unlikely.

We suspected when designing this study that mild microphthalmia might be variably reported and that this would lead to significant geographical variation. In fact our results for all cases, including mild cases, suggest that this did not occur to any great extent. Restricting the analysis to severe cases was difficult because of the unknown severity status of a proportion of cases. Nevertheless, we believe that it was helpful in determining that any geographical variation we did find, including the urban-rural gradient, was not an artefact of the variable reporting of mild cases.

Implications of the study

A geographical and clustering analysis such as that reported here is very much a first stage in looking at the environmental epidemiology of a congenital anomaly. Generalised clustering analyses may not be sensitive to some particular geographical trends, as we showed with the urban-rural gradient, and it is therefore necessary to move forward to hypothesis testing about specific exposures, whether within an ecological or case-control context. Our results are reassuring in terms of the absence of strongly localised environmental exposures causing clusters of children to be born with anophthalmia and microphthalmia, but further study is needed of the aetiology of anophthalmia and microphthalmia to prevent this condition in future generations.

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Contributors: HD coordinated the study (particularly its design and interpretation) and drafted the paper; she will act as guarantor for the paper. AB participated in the study design (particularly data collection methods and design of the questionnaire), collected the data, and participated in the statistical analysis (particularly analyses of prevalence rates). BGA supervised the statistical analysis and informed its interpretation. PW performed various statistical analyses particularly those concerning clustering.

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Conflict of interest: None.

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Correction

Short stature and Helicobacter pylori infection in Italian children: prospective multicentre hospital based case-control study

An editorial error occurred in this paper by Giuseppina Oderda and colleagues (22 August, pp 514-5). From top to bottom the fourth column of the table labelled Matched sets should have read: 2, 25 [not 225]; 16, 91 [not 1691]; 3, 51 [not 351]; 4, 76 [not 476]; 7, 62 [not 762]; 6, 59 [not 659]; 2, 60 [not 260]; 3, 69 [not 369]; 5, 23 [not 523]; 6, 100 [not 6100]; 7, 31 [not 731]; 10, 86 [not 1086]; 2, 15 [not 215]; 5, 112 [not 5112]; 1, 23 [not 123]; 6, 104 [not 6104].

Commentary: Clustering of anophthalmia and microphthalmia is not supported by the data

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Clustering is a difficult concept to define precisely. It is important to distinguish it from the notion of an individual cluster, corresponding to an excess number of cases in one small area or around a putative point source. A fundamental problem when trying to assess the significance of a specific cluster is that analysis is almost always post-hoc—that is, the cluster is recognised as being unusual by some uncontrolled process, and then a subsequent statistical assessment is made. This is exactly opposite to the situation for which statistical testing was designed—where a hypothesis is first generated and then subsequently tested on new data. As a consequence the vagaries of the spatial and temporal boundaries of the putative cluster make it very difficult to determine the probability of the event being a chance occurrence.

A key aspect of statistical analysis is the concept of replication. If there is a suggestion of clusters at a variety of locations then statistical procedures are more capable of assessing whether this is due to chance. In this sense the analysis of clustering can be viewed as an extension of methods for studying spatial variation to a much smaller scale, where classic mapping procedures no longer are applicable. However, instead of being able to produce a visually appealing map of disease incidence that varies smoothly, here the variability is too localised to allow the averaging necessary to produce such maps, and the more abstract concept of excessive variance must be relied upon.[1]

Many new problems arise in attempting to do this. The most fundamental is how to account for the variation in population density at a very fine scale. Where available a complete population enumeration can be used, but when the scale is very small often it is more accurate to use a sampling scheme for selecting (matched) controls.

A second problem is determining the appropriate metric for establishing closeness. Should it be a fixed distance, as in methods developed by Diggle et al,[2] or should the population density be considered, as in methods developed by Cuzick and Edwards,[3] so that a cluster would encompass a larger area in a low density rural area than in a built up urban area. Other differences relate to whether clusters should be determined by the distance between cases, or the number of cases in predefined geographical areas (eg, wards or postcodes). That distance methods would be more efficient would be suspected, but sometimes this approach is easier to apply to available data, and simulations suggest that the power of these methods are similar.[4]

Clustering methods will always be exploratory, and they leave open the question of what is responsible for the clusters. Their value is to identify clearly when it is worth while to search for causative (infectious or environmental) agents. As more small scale geographical information becomes available for different diseases it is likely that clustering methods will be used more widely. Not only will they help to identify when clustering is present, but as in the present example, they also can rule out localised clustering in favour of a simpler explanation in terms of population density.

1 Elliott P, Cuzick J, English D, Stern R, eds. Small-area studies: purpose and methods. In: *Geographical and environmental epidemiology: methods for small-area studies*. Oxford: Oxford University Press;1992:14-21.
2 Cuzick J, Edwards R. Spatial clustering for inhomogeneous populations. *J Roy Stat Soc B* 1990;52:73-104.
3 Diggle PJ, Chetwynd AG. Second-order analysis of spatial clustering for inhomogeneous populations. *Biometrics* 1991;47:1155-63.
4 Alexander FE, Boyle P, eds. *Methods for investigating localized clustering of disease*. Lyons: International Agency for Research on Cancer Scientific Publications, 1996. (No 135.)

An important lesson

The hazards of self management

It started with a cough, just a bit of a cold. Soon I was bringing up thick green looking sputum. The sort of stuff that patients normally delight in showing you. The cough worsened and took on that rattling, bronchitic quality.

At the time I was working as a senior house officer in Australia. I had not registered with a local doctor. I had not seen the need; after all I was working in the hospital's casualty department.

After two weeks of green phlegm production I decided that my sputum was definitely infected and that antibiotics were called for.

Finding a packet of amoxycillin in the casualty drug cupboard I took two capsules immediately. The next morning I woke up itching. Getting out of bed I looked down to see that an urticarial rash had developed on my hands and feet.

Ah ha, I thought, a drug reaction. But I had taken amoxycillin before without any ill effect. Perhaps I had glandular fever; my throat had been a bit sore. The amoxycillin tablets were relegated to the bin. I took an antihistamine tablet to ease the itching.

Arriving at work I delved back into the drug cupboard. Ah, erythromycin. I took 500mg and looked forward to the swift curtailment of my productive cough. The abdominal cramps and nausea started around eight o'clock that night. The itching seemed to get worse.

By three in the morning the cramps from the erythromycin and the itching from the amoxycillin finally ceased. The erythromycin was discarded the next day in favour of cephalexin.

That night after I returned from work my partner glanced at the antihistamine tablets I had been taking for the itching, "You know that these are two years out of date," she said. "You really shouldn't self medicate." I agreed.

Self management and medication can at the least cause minor problems, but at worst have potential for disaster.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to.