

Approaches to investigating clusters: By example, childhood leukaemia near Sellafield

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A *cluster* is an unusually high incidence of a disease during a limited time period among the population of a defined area.

The *suspicion of a cluster* will often arise from observations by an individual or group – for example, either members of the public or of the medical profession. Sometimes the suspicion will arise from examination of routine records.

The level of suspicion of an underlying hazard being responsible for a cluster of disease depends upon:

- 1) the degree of clustering,
- 2) the plausibility of an underlying hazard.

A cluster may occur because the shared environment contains a *health hazard* or through *chance coincidence*. The health hazard may be the suspected factor, if there is one, or some other confounding causal exposure.

Plan of investigation of suspected clusters

In the investigation of clusters it is helpful to follow a systematic approach. How far one progresses through the stages will depend on successive levels of suspicion and concern.

1. Investigate available medical records for suspected index cases:
 - Can the cases be identified in the records?
 - Can the diagnoses be confirmed?
2. Consider the defining features of the cluster, such as:
 - a) diagnosis,
 - b) cases or deaths,
 - c) geographical boundary,
 - d) sex,
 - e) age group,
 - f) calendar period.
 - how were these selected?
3. Are there any further relevant cases in the medical records?
4. Can the suggestion of a cluster be confirmed?
 - a) size of excess (observed/expected cases),
 - b) statistical precision of excess,
 - c) excess compared to other similar environmental areas
 - i) as observed,
 - ii) as expected under random distribution of cases.

5. How did the cluster come to attention? Had there been any prior reasons for concern? Was the disease of concern identified in advance?
6. Find out about the known causes of the disease from the medical literature:
 - If the diagnoses are not all identical is a common cause likely?
7. What is the putative cause for concern? Is there any plausibility associated with this putative cause? If relevant, has a sufficient latent period elapsed?
8. Find out about the environmental features of the index cases:
 - Do the cases share any geographical features?
 - Do the cases share any common exposures or activities?
 - If so, are these known or plausible hazards for their disease (i.e. potential confounding variables)?
9. Have there been excesses among other populations in similar areas? What is known in other countries?

Conclusions

Based on the above stages a suspected cancer cluster can be designated as:

- a) not actually present,
- b) present with definitive cause,
- c) present with putative cause,
- or d) present but no putative cause.

Actions

Depending upon which conclusion is reached the following actions are respectively indicated:

- a) none,
- b) prevention of exposure to definitive cause,
- c) epidemiological study,
- d) possible epidemiological study.

Epidemiological studies

Possible epidemiological approaches, not in order of priority, include:

- 1) Cohort study,
- 2) Case-control study,
- 3) Further detailed analysis of routine statistics.

Childhood leukaemia near Sellafield as an example

Towards the end of 1983 a suggestion was made that there was an excess of childhood leukaemia near the Sellafield nuclear waste reprocessing plant on the northwest coast of England. The following describes the findings of the subsequent investigations through the stages mentioned above.

1. The cases suggested to form a cluster were identified in either medical or cancer registration records or, where appropriate, from death certificates. The diagnoses were confirmed.
2. a) The diagnosis emphasised was childhood leukaemia although other childhood cancers were also considered.
b) Both non-fatal and fatal cases were included.
c) Although one particular village of Seascale was specifically identified, some other coastal villages had been included.
d) Both sexes were included.
e) More than one age group was presented and, in particular, the unusual age group 0–9 years was used for one statistic.
f) The calendar period attempted to cover the duration of operation of the Sellafield site.
3. One or two further relevant cases were identified in medical records.
4. The high incidence was confirmed in two different analyses – both by considering Seascale itself and also by considering a larger geographical area (Millom Rural District) including Seascale. For Seascale:
 - a) There were 4 observed cases of lymphoid malignancy compared with 0.25 expected during 1968–84 at ages under 15 years.
 - b) The excess was 16-fold, but statistically imprecise because of the small numbers involved.
 - c) i) The associated Poisson probability for this excess was smaller than for any of the other 674 electoral wards in the northern region of England.
 For Millom Rural District:
 - a) There were six observed deaths from leukaemia compared with 1.4 expected during 1968–78 at ages under 25 years.
 - b) The excess was 4-fold, but statistically imprecise because of the small numbers involved.
 - c) i) The excess was the second highest among 152 Rural Districts similar in population size to Millom.
ii) The distribution of leukaemia deaths among the 152 Rural Districts did not show any indication of departure from a random distribution.
5. The cluster came to attention through a television programme. There had been some limited prior concern, but no special studies had been completed although one was in progress. The

television company had originally proposed a programme on the health of the Sellafield workforce, but replaced it by one on the childhood leukaemia cases that they heard about incidentally. The disease of concern was not identified in advance.

6. The only widely accepted cause of childhood leukaemia is prenatal abdominal X-ray of the mother. The diagnoses were mainly acute lymphatic leukaemia.
7. The putative cause for concern was the radioactive discharges into the sea and air from Sellafield. Because the only widely accepted cause of childhood leukaemia is radiation, it could not be said that the suggestion was implausible – except that radiobiological calculations using currently accepted models suggested that the levels of discharges were far too low to cause the observed risk.
8. The cases were known largely to live in Seascale but nothing further was known from easily available records about their exposures or activities.
9. No other investigations had been carried out among other populations near nuclear installations or in other countries.

Conclusions

It was concluded that there was an excess of childhood leukaemia in the area, particularly in Seascale, although the cause was not known. The excess can thus be designated as: c) – “present with putative cause”.

Actions

Action c) was indicated, with epidemiological studies being recommended to try to assess the reasons for this excess of childhood leukaemia.

Epidemiological studies

Each of: 1) cohort study,
2) case-control study,
3) further detailed analysis of routine statistics, were recommended.

Results

The cohort study was of children born or attending schools in Seascale and was carried out partly because of the known imperfections of geographical studies. It showed that the excess of childhood leukaemia appeared to be limited to children born in the village, rather than those moving in after birth to attend one of the local schools. This suggested that if there was a localised cause then it operated very early in life or before birth. The case-control study looked at individual factors

that were thought may be related to the excess. A strong statistical association was found between fathers' exposure to external ionising radiation during employment at Sellafield before the conception of their children and the subsequent incidence of leukaemia. The association can explain statistically the Seascale excess of childhood leukaemia.

Summary

There is occasionally concern about suspected clusters of disease in geographically localised areas among members of the general public or other groups. These occurrences need a systematic approach to their investigation. Such an approach needs to consider the definition and characteristics of the cluster and of the putative environmental cause for concern. Depending on the outcome of these considerations there will be different actions, possibly involving epidemiological studies. The necessary components of the approach and resulting actions are outlined in this paper, and illustrated by the example of childhood leukaemia rates around the Sellafield nuclear plant.

Résumé

Investigations de «clusters»: Les leucémies infantiles dans la région de Sellafield comme exemple

Les «clusters» de maladie peuvent être à l'origine d'une préoccupation considérable dans la population. Quelle peut être la réaction la plus appropriée de l'épidémiologue? Une approche systématique est présentée dans cet article, depuis la caractérisation du «cluster» jusqu'à la planification d'études épidémiologiques éventuelles. Chacun de ces pas est illustré par l'exemple concret d'une situation similaire survenue dans la région de Sellafield à propos de l'accroissement des leucémies infantiles autour de l'usine de retraitement de produits nucléaires.

Zusammenfassung

Das Vorgehen bei ungewöhnlichen Krankheitshäufungen (Clusters), dargestellt am Beispiel der Häufung von Kindheitsleukämien von Sellafield

Clusters von Krankheitsfällen können in der Bevölkerung grosse Besorgnis verursachen. Wie geht

der damit konfrontierte Epidemiologe am besten vor? Es wird ein systematisches Vorgehen in Stufen vorgeschlagen, von der Überprüfung der Diagnosen und der Abgrenzung des Clusters bis zur allfälligen Planung von epidemiologischen Studien. Die einzelnen Schritte werden anhand der Häufung von Kindheitsleukämien im Umfeld von Sellafield dargestellt.

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